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THE TREATMENT OF ANURIA*

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THE early determination of the etiology of urinary suppression is frequently lifesaving. Rational and successful therapy depends largely on the clinical evaluation of a case in the first few hours of observation. Ordinary routine treatment should be altered to meet the features in a particular case. Although the division into medical and surgical problems is necessary and helpful, a more descriptive classification is that of obstructive and nonobstructive anuria. Cabot and Iber[1] define obstructive anuria as that due to obstruction of the passage of secreted urine, and nonobstructive anuria as that caused by parenchymal pathologic changes that interfere with secretion. For a more specific grouping, nonobstructive anuria may in turn be divided into anuria due to true parenchymal disease of the kidney and that due to extrarenal factors unassociated with the kidney itself. The following classification outlines the conditions most frequently encountered in urinary suppression.

I. Obstructive anuria
  A. Obstruction of vesical neck (carcinoma, calculi and prostatic hypertrophy)
  B. Ureteral and renal obstruction (calculi, inflammatory strictures, crystals of sulfonamide drugs, intrinsic carcinoma of the urinary tract, extrinsic carcinoma of the pelvic organs and abdominal tumors, trauma and misplaced sutures)
II. Nonobstructive anuria
  A. Extrarenal disease (cardiac decompensation, intestinal obstruction, peritonitis, gastrointestinal hemorrhage, medical and surgical shock), dehydration and burns
  B. Renal disease
    1. Primary parenchymal lesions (glomerular nephritis, pyelonephritis, nephrosclerosis, polycystic kidneys, toxemia of pregnancy, lipoid nephrosis and amyloid disease)
    2. Poisons (mercury, lead, cantharides, phosphorus, turpentine and oxalic acid)
    3. Nephrotoxic agents (acid hematin deposition after transfusions, black-water fever, myohematin deposition after crushing injuries and tubular deposition of sulfonamide crystals)
    4. Hepatorenal syndrome
    5. Cortical necrosis
    6. Thrombosis of renal artery or embolism

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DIFFERENTIAL DIAGNOSIS

A careful history-taking saves time otherwise spent in observation and unnecessary studies. This is particularly true in cases of obstructive anuria, usually preceded or accompanied by pain in the bladder, abdomen or regions of the kidney that points to the source of anuria. The significance of a history of stones, operations or infections associated with the genitourinary tract or of treatment of carcinoma of the cervix or bladder should be kept in mind. A history of drug consumption is easily overlooked. In cases that have been followed or are under treatment the etiology is usually easily ascertained, whereas in patients who present themselves in anuria, the history may be the only lead that one obtains.

Physical examination in many cases helps to supply the explanation. In the obstructive anurias the most frequently found abnormalities are prostatic disease in men and pelvic disease, such as carcinoma of the cervix or pelvic tumor, in women. Occasionally an abdominal tumor or enlarged tender kidneys are present.

Many of the nonobstructive anurias are quickly ruled in or out by physical examination. Vascular collapse due to loss of blood, coronary thrombosis, dehydration and diabetic coma are usually brought to light by examination. Emboluses lodging in the renal artery usually originate in the heart, where mural thromboses are formed owing to myocardial infarction, rheumatic heart disease or bacterial endocarditis, with or without ventricular fibrillation. The hepatorenal syndrome may develop without jaundice, but usually jaundice is present. In any patient who presents jaundice and anuria, this syndrome ought to be kept in mind. Cortical necrosis is most commonly found following pregnancy or as a result of trauma, although it has been known to occur after a minor operation. Electrolyte imbalance (retention or depletion of sodium chloride) may show itself in either edema or dehydration, but the imbalance is secondary to some other disease such as nephritis in retention or gastrointestinal disease with vomiting in depletion. The findings in

primary renal disease are well known and need no comment here.

Diagnosis may depend on accessory data. A plain abdominal x-ray film should always be made in obscure cases of anuria. Unsuspected calculi and abdominal or renal tumors may give the clue to the diagnosis. Occasionally an intravenous pyelogram gives valuable information at the onset of urinary suppression; it may be obtained with safety if the nonprotein nitrogen is not over 60 mg. per 100 cc. In general, intravenous pyelograms give little information when the nitrogen retention is above this figure. If the diagnosis is in doubt, one should not hesitate to obtain cystoscopic examination and retrograde pyelograms with Diodrast, Skiodan or Hippurin. Sodium iodide as a retrograde dye should not be used, since it is irritating. The risk of a skillfully performed procedure is slight when balanced against the precise information that one obtains. The need for retrograde pyelography is exemplified by the difficulty one may have in differentiating ureteral obstruction due to sulfonamides from tubular obstruction due to transfusion reactions occurring in a case under sulfanomide therapy.

The laboratory data of particular value are the composition of the urine, the levels of nonprotein nitrogen, protein, chloride, sodium and sugar in the serum or blood and the carbon dioxide combining power or content of the plasma. The most impressive finding in the urine is of course gross hematuria, but it is usually present when the diagnosis of the underlying disease is relatively simple—for example, tumors encroaching on and eroding the mucous membrane of the genitourinary tract or the presence of kidney stones. Hematuria is ordinarily absent preceding extrarenal anuria, although initial hemoglobinuria is sometimes seen. Primary parenchymal renal disease rarely exhibits gross hematuria. This is true also of poisons and nephrotoxic agents, where anuria is frequently preceded by hemoglobinuria and cortical necrosis. In 117 cases of renal infarction reported by Hoxie and Coggin[2] gross hematuria occurred in only 4 (3 per cent), whereas microscopic hematuria was observed in 35 (30 per cent). The value of white cells and casts in the absence of dehydration and of red cells at any time are evident. A nonprotein nitrogen level in excess of 40 mg. per 100 cc. is considered elevated and warrants a search for the etiology. Serum protein levels below 5 mg. are often accompanied by edema, sometimes associated with edema of the kidney, albuminuria and decreased kidney function. Sodium and chloride are lost in considerable amount in vomiting and result in dehydration (see discussion of Case 3). Retention of sodium chloride, as in primary renal disease, may further increase edema by causing retention of fluids. A sodium chloride level in whole blood exceeding or lower than 450 to 500 mg. bears consideration, in both the etiology and the treatment of renal failure.[3] Anuria may be present in diabetic acidosis when the carbon dioxide plasma content falls below 20 vol. per cent. Hyperglycemia without acidosis, except experimentally and in the rare cases in which intravenous glucose is indiscriminately administered in large amounts, does not cause anuria.

Treatment

Obstructive anurias are usually due to vesical or ureteral blockage. In obstruction of the vesical neck the processes are usually of long standing, and in such cases gradual decompression is desirable. During the preliminary decompression the general condition may be improved by transfusions and intravenous salt solutions, so that if operative procedures are later necessary they can be carried out with less risk. When ureteral obstruction is present, catheterization of the ureters may relieve the obstruction. At times ureterostomy or nephrostomy is necessary as a temporary procedure to relieve obstruction and to allow the return of renal function. When conditions permit, removal or correction of the primary cause of obstruction may be done, as in ureteral blockage from carcinoma of the bladder. In general, even dangerously ill patients stand necessary procedures on the kidneys or ureters for relief of obstruction remarkably well, and improvement begins quickly with the onset of diuresis. It is not unusual for patients with a high nonprotein nitrogen (200 to 300 mg. per 100 cc.) and generalized edema to recover rapidly if the obstruction is acute and little chronic renal disease exists.

Postoperative care is principally a matter of the proper administration of fluids, guided in particular by frequent determinations of the nonprotein nitrogen and chloride. Occasionally peripheral vascular collapse occurs, following a genitourinary operation. At times this condition is puzzling and persistent and in spite of plasma or transfusions lasts for several days. In such cases active measures to combat shock must be unremitting, for if shock is long continued, degenerative tubular disease of the kidneys may result. A lowered serum protein level and anemia should be corrected by transfusions of whole blood or plasma. Low blood chloride levels should be corrected by the giving of intravenous normal or hypertonic salt solution.

A frequent mistake in therapy is the aimless administration of intravenous fluid. Dehydration should be corrected rapidly, but fluid should not be given to the point of producing edema. The administration of fluids should be governed by the rate of renal excretion and by the level of the nonprotein nitrogen and chloride. If the chloride is normal in the presence of dehydration a 5 per cent dextrose solution in distilled water should be used. If excess fluid is given in the absence of renal excretion in older patients, the circulation may be embarrassed and may further interfere with restoration of renal function.

The nonobstructive anurias are more frequent than the obstructive. Of 78 cases collected by Cabot and Iber[1] only 29 were due to obstruction of urinary outflow. In extrarenal anuria, the presenting complaint is usually not lack of urine but a group of symptoms that point to some other underlying disease, although Segal and Read[3] reported 2 cases with gastrointestinal perforation without symptoms other than anuria. In these cases the anuria served only to obscure the true condition. Hemorrhage from the gastrointestinal tract, cardiac failure, diabetic coma and dehydration from nausea, vomiting or diarrhea, however, are usually fairly obvious. The occasional development of severe oliguria or anuria in such cases may complicate the clinical picture, and certainly makes treatment more difficult.[4] This secondary nitrogenous retention is so severe in some cases as to be the actual cause of death.

In primary renal disease treatment produces less dramatic results. The various measures used to promote diuresis are well known. The administration of diuretics, together with a salt-free diet, and the giving of limited fluids in the presence of edema usually constitute the treatment. The most frequently encountered renal poison is bichloride of mercury. Early administration of sodium formaldehyde sulfoxalate may be helpful; otherwise supportive treatment is necessary. The early peripheral collapse seen in these patients may be prevented by the giving of intravenous salt solution, glucose solution or plasma. Usually within forty-eight hours there is nitrogen retention, sometimes associated with lowered chloride and diminished alkali reserve. Talbott and his associates[5] suggest the use of alkali, since the effectiveness of sulfoxalate is thus enhanced and since the alkali reserve is in part depleted.

Nephrotoxic agents are not infrequently seen in hospital practice,[6] where transfusions and sulfonamides are so widely employed. When hemolysis occurs as the result of transfusion reactions, acid hematin is precipitated in the kidney tubules. Many workers advise the preliminary administration of sodium bicarbonate by mouth to assure an alkaline urine for prevention of this precipitation in case hemolysis occurs. This is especially valuable when difficulty has been encountered in obtaining a perfect cross matching prior to transfusion. After such an accident occurs, the early administration of intravenous sodium bicarbonate or lactate may be lifesaving. Once precipitation occurs, little can be done. Even then, however, it is worth while to administer intravenous salt solution or sodium lactate to keep the uninvolved tubules functioning. As a rule the sulfonamides are crystallized in the pelves of the kidneys or in the ureters as well as in the tubules. In such cases catheterization and lavage of the ureters and pelvis are extremely satisfactory in dislodging the loosely conglomerated crystalline deposits. The sulfonamides may cause hemolysis and produce the same train of events as that seen in hemolysis from transfusion reactions. During the present war occasional cases of kidney tubular obstruction have been seen following crushing injuries. This may be due to the deposition of myohemoglobin formed in the crushed muscles. It has been suggested that the tubular damage in these cases is of a chemical nature, and that the danger of renal failure in patients subjected to crushing injuries should be anticipated and prevented. The application of a tourniquet to the injured limb and re-establishment of circulation have been advised as soon as measures were taken to produce diuresis. Measures to prevent tissue breakdown, such as packing the extremity temporarily in ice, may be helpful. Alkalization is suggested.[7]

The hepatorenal syndrome is still a poorly understood phenomenon. Nitrogen retention and even anuria are occasionally found in patients with liver disease, with or without jaundice. This syndrome should therefore be anticipated and thus prevented in cases with gall-bladder disease and primary liver disease.[8] Every patient presenting himself for gall-bladder surgery should have a critical appraisal of renal function. Prevention of nitrogen retention may be managed by adequate fluids, if not by mouth then intravenously. The carbohydrate intake should not fall below 150 gm. in twenty-four hours.

Cortical necrosis of the kidneys is occasionally seen post partum and following severe — usually abdominal — trauma.[9, 10] Previous writers have said that the disease is always fatal.

Thrombosis of the renal arteries with renal infarction is occasionally seen as the result of emboli from the left side of the heart. There is little to do when this occurs save to support the patient generally and to prevent shock.

Decapsulation has been advised for anuria due to transfusion reactions and in particular to bichloride poisoning. Talbott[6] mentioned a case that one of us (W. F. L.) had an opportunity to follow and that gave evidence of the futility of decapsulation in restoring renal function after such reactions. On the fourth day of anuria the ureters were catheterized and the right kidney was decapsulated. A flow of urine began twenty-four hours after operation. No difference in urine volume was shown between the two kidneys. Six weeks later, when a normal urine volume and nonprotein nitrogen level were present, clearance tests with inulin and Diodrast were done with catheters in each kidney. There was no notable difference in function between the kidneys.

Several cases of urinary suppression have been encountered that illustrate points of interest in the management of anuria. Reports of these cases follow.

CASE 1. *Anuria due to postoperative degenerative tubular changes.* A 71-year-old man was admitted to the hospital with acute retention of urine that had been present for a few days. Prior to admission catheterization had been done and a large amount of urine withdrawn.

At physical examination the blood pressure was 150/70. The heart and lungs were normal. A right indirect inguinal hernia was present. A markedly enlarged (Grade 3), smooth, elastic prostate was present. There was penile hypospadias.

The patient was catheterized, and the small amount of urine present in the bladder was withdrawn. The urine showed a specific gravity of 1.023, a slight trace of albumin and no sugar. The sediment contained scattered white and red cells but no casts. The nonprotein nitrogen was 35 mg. per 100 cc. The hemoglobin was 93 per cent (Sahli), the red-cell count 4,940,000, and the white-cell count 17,000.

Cystoscopic examination revealed a markedly trabeculated bladder and large lateral prostatic lobes. Since the patient's general condition was excellent, and since it was thought that no improvement could be expected from continued catheter drainage, a perineal prostatectomy was done. Immediately after operation the patient's condition was good, but a few hours later a severe hemorrhage into the bladder occurred. Since the perineal bag and the urethral catheter could not be irrigated, a suprapubic cystotomy was done under local anesthesia, bleeding being controlled by a Hagner bag. The blood pressure fell to 60/40. Two transfusions of 500 cc. each were given, and the blood pressure gradually rose to 110/60 during the next 24 hours. On the 1st postoperative day, however, the blood pressure ranged from 80/40 to 90/60 despite the intravenous administration of glucose solution, normal saline solution and stimulants. For the next 4 days the systolic pressure remained below 120, and during the 5 days after operation there was practically no urinary secretion. The nonprotein nitrogen rose to 153 mg. on the 3rd postoperative day. During this time 14,000 cc. of 5 or 10 per cent glucose in normal saline solution or distilled water was given intravenously, and on one occasion 50 cc. of 50 per cent glucose was given without effect. Edema appeared. The hemoglobin dropped to 58 per cent, and the serum protein to 4.8 mg. per 100 cc. The urinary secretion was 900 cc. on the 5th postoperative day and between 1000 and 3100 cc. during the following week. Despite this apparent improvement the nonprotein nitrogen rose to 245 mg. On the 12th postoperative day the patient developed bronchopneumonia. Oliguria developed and was followed by coma, and death occurred on the 17th postoperative day. The carbon dioxide content of the plasma at one time reached 32 vol. per cent but did not go below this figure. The sodium chloride level remained within normal limits.

Post-mortem examination showed pneumonia of the left lower lobe, healing ischemic necrosis of the liver and acute tubular degeneration of the kidneys. There was marked dilatation of the kidney tubules, with some areas showing regeneration.

This patient stood the operation well. The serious secondary hemorrhage with prolonged shock seemed to be the cause of the renal failure. The blood pressure was below or barely at the secretory level for about twenty-four hours. One can assume on the basis of the microscopic study of the kidneys that there was no appreciable chronic renal disease and that therefore the anuria resulted from the continued low blood pressure, acute degenerative changes associated with ischemia, an acid-base disturbance of the blood or a transfusion reaction. On the basis of blood chemical findings an acid-base disturbance can be excluded. For a time the possibility of transfusion kidneys was considered, but this was ruled out by autopsy. It is concluded that an acute degenerative process of the tubular epithelium associated with or due to poor circulation resulting from continued low blood pressure was the mechanism that prevented prompt recovery of kidney function after the initial anuria. Some chronic back-pressure changes may have played a part. The low specific gravity of the urine after operation tends to support the assumption that the tubules concentrated poorly. Death resulted from terminal pneumonia and circulatory failure, since kidney function was improving even after death seemed inevitable. The chief point of interest in the case is the cause of tubular degeneration.

How could this case have been treated better? Of course, the obvious answer in such cases is to prevent, or at least to recognize and arrest, hemorrhage before serious shock develops. Occasionally, as in this case, the bleeding is so sudden and profuse that much blood is lost in the bladder before it can be recognized and treatment instituted. The blood loss was extreme, because even after two transfusions the hemoglobin was only 58 per cent. More transfusions shortly after the first two or, still better, the administration of plasma instead of intravenous fluids might have prevented continued shock and kidney damage.

CASE 2. *Anuria due to ureteral stones and a solitary kidney.* A 52-year-old woman had a left nephrectomy performed by one of us (W. F. L.) in December, 1940, necessitated by a calculous pyonephrosis. An intravenous pyelogram showed a normally functioning and appearing right kidney. The right ureter was not catheterized for fear of introducing infection. Owing to the patient's poor general condition the left ureter, which contained a large stone, was not removed. Because of persistent infection in the urine and pain in the left lower quadrant of the abdomen, the left ureter was removed in March, 1941. Up to that time the patient had had no symptoms referable to the right kidney. Following the ureterectomy she was given a course of sulfathiazole therapy. The urine became clear. She remained well until June 13, 1940, when she was seized with sudden, sharp pain in the left upper quadrant of the abdomen and the flank. This was followed by chills, fever, nausea and vomiting.

On admission to the hospital the temperature was 105°F., the pulse 124, and the respirations 28. There was generalized edema. The patient was irrational and obviously very ill. The lungs were clear. The heart sounds were rapid and weak but otherwise normal. The blood pressure varied between 75/40 and 50/25. The abdomen was distended, and muscle spasm and tenderness were present in the right upper quadrant and the flank. The kidney could not be palpated.

No urine was present in the bladder. The hemoglobin was 76 per cent, the red-cell count 4,030,000, and the white-cell count 12,700. The nonprotein nitrogen was 65 mg. per 100 cc., and the blood chloride level was 507 mg. per 100 cc. A plain abdominal x-ray film was relatively unsatisfactory owing to gas-filled intestines, but no calculi were visible.

It was obvious that the cause of anuria must be determined quickly, and accordingly a cystoscopy was done on the day of admission. A catheter passed quite easily to the level of the right kidney, but no urinary drainage took place. It was possible to inject 10 cc. of fluid through the catheter and to recover most of it, so that it was assumed that the eye of the catheter rested in the renal pelvis. The catheter was left in place during the night. Five per cent glucose solution was given intravenously and caffein with sodium benzoate was used. The blood pressure remained at 60/40, and no urine was obtained by ureteral catheter or from the bladder.

The next day there was no improvement in the general condition. The nonprotein nitrogen was 92 mg. per 100 cc., the blood chloride 531 mg., and the carbon dioxide content of the plasma 40 vol. per cent. The cause of anuria was puzzling, but it was necessary to assume an obstruction, unless an unusual situation, such as cortical necrosis or occlusion of the renal artery and renal infarct, had occurred.

Exploration of the kidney was therefore carried out under nitrous oxide, oxygen and ether anesthesia. When the upper ureter was exposed, a group of small stones were palpated and easily removed. The ureter below this level was explored and found to be patent. A large catheter slipped up into the renal pelvis, but no urine was obtained. The kidney itself looked and felt normal. A catheter ureterostomy was done, and the patient stood the operation well. A transfusion was given and was followed by intravenous injection of 1000 cc. of a 5 per cent glucose in saline solution.

The state of shock persisted. No urine was secreted. Two cubic centimeters of adrenocortical extract was given every 3 hours. The blood pressure quickly rose to 110/60 and urine was secreted. The adrenocortical extract was continued for 36 hours, during which time the blood pressure rose to 160/100, where it remained for several days, returning later to the normal level of 135/80. Following the onset of urinary secretion 540 cc. was passed in the first 24 hours and 1800, 3300 and 3900 cc. on successive days. The nonprotein nitrogen was normal 1 week after operation. Follow-up x-ray examination showed some hydronephrosis but no calculi. The ureterostomy catheter was removed on the 13th postoperative day, and the wound was healed by the 21st day. The patient was discharged 23 days after operation and has since remained well.

shock. In this case a preoperative diagnosis of calculi blocking the ureter was not made, but it could have easily been made with a pyeloureterogram. It was thought that the ureteral catheter had passed to the kidney pelvis and that therefore the cause of anuria was not obstruction. Exploration of the kidney seemed the only course and was fortunately successful. Although the patient's condition was poor, operation affected her but little. The continued state of shock was the obvious cause of anuria once the obstruction had been relieved. The usual methods for treatment of shock were of no avail. In this case adrenocortical extract used empirically seemed lifesaving, although one wonders what the course would have been if it had not been used. It should be noted that hypertension persisted for some days thereafter. After diuresis was well established, sulfathiazole in small doses was given, with prompt disappearance of the fever.

TABLE 1. *Summary of Data in Case 3.*

Hosp. Day	Clinical Course	Parenteral Intake	Output	Blood Sugar	Blood N.P.N.	Plasma Carbon Dioxide	Hemoglobin	Insulin	Urine
		cc.	*cc.*	*mg./100cc.*	*mg./100cc.*	*vol. %*	*gm./100cc.*	*units*	
	Blood pressure 90/70; spinal fluid normal.	1500 (saline by clysis)	0	342	95	50	16.2	10 (cryst.) 20 (prot.)	
1	Blood pressure 140/80; patient semicomatose.	1500 (saline by clysis) 1000 (5% glucose i.v.)	30 (catheter)	317 263	108	—	—	10 (cryst.) 20 (prot.)	S.g.1.017; v.s.t. albumin; no sugar; many white cells and 1-3 red cells.
2	Patient drowsy	3000 (2.5% glucose i.v.)	850	400	110	—	—	40 (cryst.) 20 (prot.)	No sugar; no casts; 8-10 white cells and 10-15 red cells.
3	Patient improved and less drowsy	2000 (2.5% glucose by clysis) (postoperatively)	1950	—	—	—	—	10 (cryst.) 20 (prot.)	No sugar
4	Patient improved; food taken	2000 (2.5% glucose by clysis)	1900	183	70	—	—	6 (cryst.) 20 (prot.)	No sugar
5	Patient greatly improved	2000 (2.5% glucose by clysis)	1300	—	—	—	—	20 (prot.)	No sugar
6	Patient rational and eating well	0	1100	154	—	—	—	20 (prot.)	No sugar
7		0	800	—	—	—	12.2	16 (prot.)	T. of albumin; no sugar; 8-10 white cells; no red cells or casts.
10		0	—	140	28	—	—	12 (prot.)	
14		0	—	—	—	—	—	12 (prot.)	Phenolsulfonephthalein excretion: 24% in 15 min. and 40% in 2 hr.
15		0	—	143	28	—	—	12 (prot.)	

There are several interesting points brought up by this case. What was the cause of the shock that made the case so difficult to treat? We do not recall a case of a blocked ureter by stone when the kidney involved was solitary or when the opposite kidney was normal with associated shock. In fact, one would suppose that a compensatory mechanism would produce hypertension. In a recent case similar to the one reported above in which anuria resulted from blockage of a solitary kidney by a stone at the ureteropelvic juncture, a compensatory hypertension was noted that disappeared when the stone was removed.

The cause of shock may have been pain, although in this case it was apparently not so severe as to cause shock. Toxemia from an acute infection may have been the cause, but a similar infection involving one or two kidneys would not likely result in

CASE 3. *Anuria due to extrarenal azotemia.* A 59-year-old woman had had diabetes mellitus for 9 years. Eight months prior to admission she had a small cerebral thrombosis, from which she recovered without noticeable residual. Following recovery she remained relatively well. The urine had been practically free of sugar on a diet without insulin.

During the 5 weeks before admission the patient felt generally weak and found it necessary to spend much of the time in bed. During this period she felt unable to do much for herself at home and received little care. She grew weaker, but had no definite symptoms until 5 days before admission, when she began to vomit. She did so four or five times a day, and as a result was able to take little fluid or food. She became sleepy and a little short of breath. There was some dizziness. The day before admission she developed weakness of the left arm and leg.

On admission the patient could scarcely be aroused. The blood pressure was 90/70, the temperature 98°F., the pulse 120, and the respirations 28. The skin was loose and dry. The pupils were slightly irregular and myotic. The mucous membranes were dry. The nose and throat were clear, and the thyroid gland was normal. The heart was not enlarged; the rate was regular and no murmurs were heard. Numerous moist rales were heard throughout both lung fields. The

abdomen was soft, and no masses were felt. Arteriosclerosis of moderate degree was present. The left arm and left leg were flaccid, and clonus was present in the left arm.

The blood sugar level, the carbon dioxide combining power and the nonprotein nitrogen were tested and when the results were reported half an hour later the patient was given 10 units of crystalline insulin and 20 units of protamine insulin. A lumbar puncture showed the spinal fluid to be normal. The patient gradually recovered consciousness and continued to improve with the parenteral administration of normal saline solution, followed later by glucose solution (Table 1). The paralysis improved slightly. She was discharged from the hospital with no apparent residual except the paralysis.

The extreme dehydration, initiated by inadequate care at home and perpetuated later by nausea and vomiting, almost resulted in death. This case represents one of the most satisfactory of the extrarenal azotemia group. Although figures on the levels of sodium and chlorides are not available, it is certain that with five days of vomiting reduction in these electrolytes occurred. As Gamble[11–13] has shown, the electrolytes largely determine the volume of body fluids, and dehydration is a secondary phenomenon in an adjustment process whereby the osmotic pressure of the extracellular and intracellular fluids is kept in proper relation. The chlorides can be replaced in part by bicarbonate, but no source of intrinsic sodium is available and this substance must be replaced, when lost, from an extrinsic source. Ginsburg[14] showed in his case that administration of fluids is not enough to ensure recovery. In fact, the administration of isotonic glucose solution alone may do harm through the production of a so-called "electrolytic vacuum" into which diffusion of sodium and chloride occurs, with further depletion of the body store. The nitrogen retention in such cases is secondary to peripheral circulatory failure, with reduction in effective glomerular filtration. The nonprotein nitrogen may be further increased by protein catabolism associated with starvation. It thus appears that the primary requisite in the treatment of such a case as this is the administration of saline solution. Glucose solution should be employed only when adequate replenishment of sodium and chlorides has occurred.

CASE 4. *Anuria due to extrarenal azotemia in the presence of chronic nephritis.* A 66-year-old woman was admitted to the hospital on February 3, 1941, in a comatose state. She was markedly dehydrated. One year prior to admission she had begun to have anorexia and loose, bloody, mucus-containing stools four or five times a day. She had lost about 25 pounds in weight. Six weeks prior to admission she was found to have a polyp of the sigmoid and was referred to the hospital for operation. During the 3 or 4 days prior to admission she had had a good deal of vomiting and had grown progressively weak.

On admission the blood pressure was 120/70. The eyegrounds were normal. Bilateral basal rales were heard in both lung fields. The heart was normal in size, but a harsh systolic murmur was heard over the entire precordium. A tentative diagnosis of extrarenal azotemia was made. With the degree of dehydration as a result of diarrhea it was difficult to determine how much renal damage was present. Saline solution and 5 per cent glucose solution were repeatedly given intravenously. For the first 48 hours the patient's condition was unchanged, but thereafter she began to improve and continued to do so. Large amounts of mucus were passed by rectum, but despite the fact that the amount passed sometimes exceeded 1000 cc., it was possible to maintain an adequate degree of hydration.

TABLE 2. *Summary of Data in Case 4.*

Hosp. Day	Clinical Course	Intake	Output	Blood N.P.N.	P.S.P. Excretion	Blood Chloride	Plasma Carbon Dioxide	Urine
		cc.	*cc.*	*mg./100cc.*	*%*	*mg./100cc.*	*vol. %*	
	Blood pressure 120/70; basal rales; patient comatose and dehydrated.	2000	300	—	—	—	—	Albumin 40 mg.; 4-3 red cells.
1	Patient's condition unchanged	4200	2400	239	Tr. (¼ hr.) 25 (2 hr.)	—	—	
2	Blood pressure 120/70; basal rales; fluids by mouth; patient lethargic but not dehydrated.	4200	1800	195	—	342	37	
3	Patient semilethargic but slightly improved	4000	1500	188	—	384	43	
4	Patient improved	4500	1800	135	5 (¼ hr.) 27 (2 hr.)	460	—	Albumin 50 mg.; many red and white cells.
5	Patient rational and much improved; pyelograms normal.	6000	2400	102	—	560	—	
6	Continued improvement	6000	2400	—	—	—	—	
7	Temp. 100°F. (? infection of urinary tract following pyelography)	3900	600	63	Tr. (¼ hr.) 2 (2 hr.)	597	—	Many white cells
8	Chill and temp. 102° F. (? urinary infection); sulfathiazole (4.3 gm.).	4000	600	63	—	540	—	
9	Patient lethargic; ureters catheterized (no obstruction); sulfathiazole (6 gm.).	4200	300	66	—	516	—	Sulfathiazole crystals and red cells
10	Sulfathiazole (1 gm.)	4000	0	85	—	—	—	
11	Coma and death		0	—	—	—	—	

Table 2 illustrates the changes that occurred in the urinary output, the nonprotein nitrogen, the phenolsulfonephthalein excretion, the serum chloride, the plasma carbon dioxide and the urine. Concomitant with the fall in nonprotein nitrogen, the hemoglobin level and the red-cell count also fell from 126 per cent and 6,670,000, respectively, on admission to 96 per cent and 4,640,000 on the 7th hospital day, when the nonprotein nitrogen reached its lowest level (63 mg. per 100 cc.).

On the 5th hospital day the patient was rational. She seemed strong and was able to take some fluid and food by mouth. It was thought at that time that she would continue to improve and that eventually she might be prepared for operation. However, the stationary phenolsulphonephthalein excretion and the drop in urinary output to 600 cc. were not taken into full account.

On the 7th day the patient had a slight fever, and on the following day she had a shaking chill. The latter was thought to be due to a urinary infection and she was given sulfathiazole. She received 11.3 gm. (170 gr.) in the ensuing

48 hours, but failed to improve. Oliguria became severe, and the ureters were catheterized to be certain that no obstruction was present as a result of chemotherapy. The patient lapsed into coma shortly thereafter, became anuric, and died on the 11th day.

It was thought that sulfathiazole therapy might have had something to do with the secondary oliguria, but actually the output decreased and the nonprotein nitrogen became stationary prior to the institution of sulfathiazole therapy.

At autopsy a large, fungating carcinoma of the rectosigmoid, measuring 12 cm. in diameter, was found. The surfaces of the kidneys were granular and marked by numerous, small, clear cysts. A number of shallow scars were present on each kidney surface. The aorta showed marked calcification, particularly in the abdominal portion. On microscopic examination cholesterol deposits were found in the coronary arteries. The glomeruli of the kidneys showed considerable variation in size, and many were scarred and contracted, a few being completely obliterated. There were a few areas where recent tubular degeneration had occurred.

This case illustrates the great changes that may occur in a patient with pre-existing renal disease when an extrarenal factor is superimposed. The patient may well have lived for some time had the kidneys, which were already damaged, not had this extra burden to combat. This case affords a contrast to Case 3, in which the kidney function returned to normal and in which no chronic kidney disease was apparent.

Case 5. *Anuria due to chronic glomerulonephritis.* A 62-year-old woman had had diabetes mellitus for 6 years. When first seen in 1939 she had slight dyspnea on exertion, with occasional cough. On physical examination the blood pressure was 170/80 and the weight 170 pounds. The heart was enlarged to the anterior axillary line and a loud apical systolic murmur was heard. The lung fields were clear. No edema was present. The nonprotein nitrogen was 23 mg. per 100 cc. The urine showed a specific gravity of 1.007, — a slight trace of albumin and no sugar. The sediment contained 2 to 3 white cells per high-power field. A phenolsulfonephthalein test showed excretions of 6, 12 and 33 per cent in ½, 1 and 2 hours, respectively.

The patient was next seen on June 28, 1940, complaining of gradual loss of vision in the preceding 6 months. She was unable to read. The pupils were too small to permit ophthalmoscopic examination. The urine showed a specific gravity of 1.010 and 100 mg. of albumin. The sediment contained 8 to 10 hyaline casts or finely granular casts per high-power field, no blood and many white cells, both single and clumped.

The patient was next seen in March, 1941, when following a severe cold 2 weeks previously she was found by her physician to have albuminuria. She began vomiting occasionally and noticed some swelling of the feet. Oliguria had been noted several weeks before admission. At admission on March 22, the blood pressure was 172/92. The heart was enlarged to the left anterior axillary line, the rhythm was regular, and a systolic murmur was heard. There was no friction rub present. There was edema of the sacrum and of the ankles, and slight ascites was present. The urine showed a specific gravity of 1.011, and a normal reaction, with a trace of albumin. The sediment showed no casts, rare red cells and 3 or 4 white cells per high-power field. Later many red cells were found. The nonprotein nitrogen was 125 mg. per 100 cc. The patient was given 5 per cent glucose solution intravenously on several occasions. The urinary volume remained low, however, and the largest volume during a 24-hour period in 2 weeks' time was 300 cc., with a daily average of 100 cc. The nonprotein nitrogen gradually increased from 125 to 180 mg. over a period of 10 days in the hospital. Despite this she remained fairly comfortable and intelligible up to the last 5 days of her illness. For the last 48 hours of her hospital course she was completely anuric. Additional chemical data showed the serum protein to be 5.2 gm., the albumin-globulin ratio 0.68, and the blood chloride 420 mg.

Autopsy showed chronic glomerular nephritis.

This case illustrates the relatively slow onset of symptoms from urinary suppression in patients with chronic nephritis. Although for a period of two weeks this patient had increasing suppression of urine, she did not feel sick enough to visit the hospital until this period of time had passed. This case is in contradistinction to the obstruction anurias, in which the course is stormy practically from the outset. The duration of life after the onset of anuria in cases of nephritis is usually less than a week. This is shorter than the duration of life after obstruction occurs, which is apparently due to the changes that have already taken place before stoppage of urine occurs. Kutzmann[15] stresses the relative comfort of patients with primary renal disease.

Case 6. *Anuria associated with obstructive jaundice.* A 67-year-old woman first noted gas on the stomach in the evening, relieved by eructation, several months prior to admission. Shortly thereafter she developed cramps in the right upper quadrant of the abdomen lasting for 12 hours and followed the next day by chills, a temperature of 103°F. and clay-colored bowel movements. She entered the hospital with jaundice. The extent of jaundice was not reported, but she was known to have had clay-colored stools. Oral gall-bladder dye showed a nonfunctioning gall bladder. Within the course of 24 hours after admission suppression of urine gradually developed and the nonprotein nitrogen was found to be 82.5 mg. per 100 cc. The urine was positive for bile, with a slight trace of albumin. The sediment was negative.

The patient was given intravenous normal saline solution and glucose solution intravenously. There were 24 hours during which no urine was passed. The jaundice began to improve spontaneously, and associated with this urine was passed and there was a gradual decrease in the nitrogen retention.

Four days after treatment was started the nonprotein nitrogen had dropped to 60 mg. and 3 weeks later it was 17 mg.

The patient was first seen by us 3 months following this episode, with a complaint not directly related to the above. In the course of therapy, however, an intravenous pyelogram was done. This showed poor renal function on each side. The output of dye was not sufficient for adequate delineation of structures. There was no calcification. A phenolsulfonephthalein test showed excretions of 21, 8 and 10 per cent in ½, 1 and 2 hours respectively. The urine had a specific gravity of 1.020, with a slight trace of albumin and no bile. The sediment showed 13 to 14 white cells per high-power field but no red cells or casts. The nonprotein nitrogen was 37 mg. per 100 cc. An electrocardiogram was normal.

This case illustrates the urinary suppression not uncommonly seen in patients who develop jaundice in the presence of pre-existing renal damage. Thompson, Frazier and Ravdin[16] believe that in obstructive jaundice associated with evidence of poor renal function there usually exists a renal lesion that is complicated by cholemic nephrosis. They demonstrated a high incidence of glomerular lesions at autopsy, and these changes predominated in elderly patients. The main lesion associated with the hepatic disorders was dilatation and compression of the lining epithelium, with various secondary changes. These authors emphasize the necessity of care as regards the renal function in such cases, since the latter may be the determining factor in improvement. Bartlett[8] mentions the rarity of nephritis associated with other diseases of the abdominal viscera.

The best treatment is prevention by adequate administration of fluids and early relief of jaundice. Essentially the treatment after oliguria has developed consists in the intravenous administration of glucose, at least 1500 cc. of 5 per cent solution daily, in an attempt to initiate diuresis. The blood sodium chloride level should be followed and kept within the normal limits of 450 to 500 mg. per 100 cc.

Summary

The etiology, diagnosis and treatment of anuria are outlined.

The importance of frequent complete blood chemical determinations and the proper administration of fluids, as to both type and quantity, are emphasized. Excessive fluid by vein in anuria may be harmful, and when fluid is given the quality and quantity should be given consideration.

Six cases are discussed in detail. These illustrate various points in the management of anuria. It seems obvious that in most cases early treatment, in the absence of severe chronic renal disease, should result in recovery.

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DR. SAUL TCHERNICHOVSKY, 1875-1943

A Hebrew Medical Poet Laureate

HARRY A. SAVITZ, M.D.*

BOSTON

A poet alone has the qualifications to represent worthily that which is great and heroic in a people.
— Maurice Maeterlinck.

DR. SAUL TCHERNICHOVSKY was a doctor of medicine by profession and practiced with distinction all through his life, but his fame rests on the fact that he was the uncrowned king of modern Hebrew poetry. For nearly half a century, Bialik and Tchernichovsky were the renowned Hebrew poets. During the last decade, the laurels of the so-called "Hebrew poet laureate" were worn by Dr. Tchernichovsky.

The Hebrew poet laureate holds no official position, nor does he receive even the minimal salary of the British poet laureate, that of a barrel of wine and £120 a year. But his dignity and honor are none the less, and perhaps even more. The Hebrew poet laureate is neither appointed nor elected. But instinctively there is a feeling among his fellowmen that he is "the" poet. Somehow they sense that he is their spokesman; his views express their remote hopes, as well as their present sorrows. It appears as though his pen were dipped in their blood and that he more than any other reveals to the world their innermost woes and pangs, as well as their aspirations and hopes. His poetry may symbolize the very period they are living in, and speaks the language that is so typically their own. On reading this poetry one experiences the feeling that it is what he himself would have said had he the ability to so express it. Such a poet was Bialik. He symbolized the Hebrew Renaissance with all its complexities. On the other hand, a poet may in a sense be the reincarnation of a period in the past history of a people and so remind them of their forgotten historical task. He may speak a language to which they are not accustomed, yet the people feel in these poetic creations the echoes and reverberations of their poets and prophets. Such a poet was Dr. Tchernichovsky. So when the great poet laureate of the Jewish people, Chaim Nachman Bialik, died in 1934, the laurel, so to speak, was placed on the head of Dr. Tchernichovsky, and he held it with dignity until his death on October 14, 1943. For in his poetry his people finally found the revival of their national instincts and historic trends. He portrayed to the world their heroic past. They felt about him what Maurice Maeterlinck said of the great Belgian poet, Emile Verhaeren, "A poet alone has the qualifications to represent worthily that which is great and heroic in a people."

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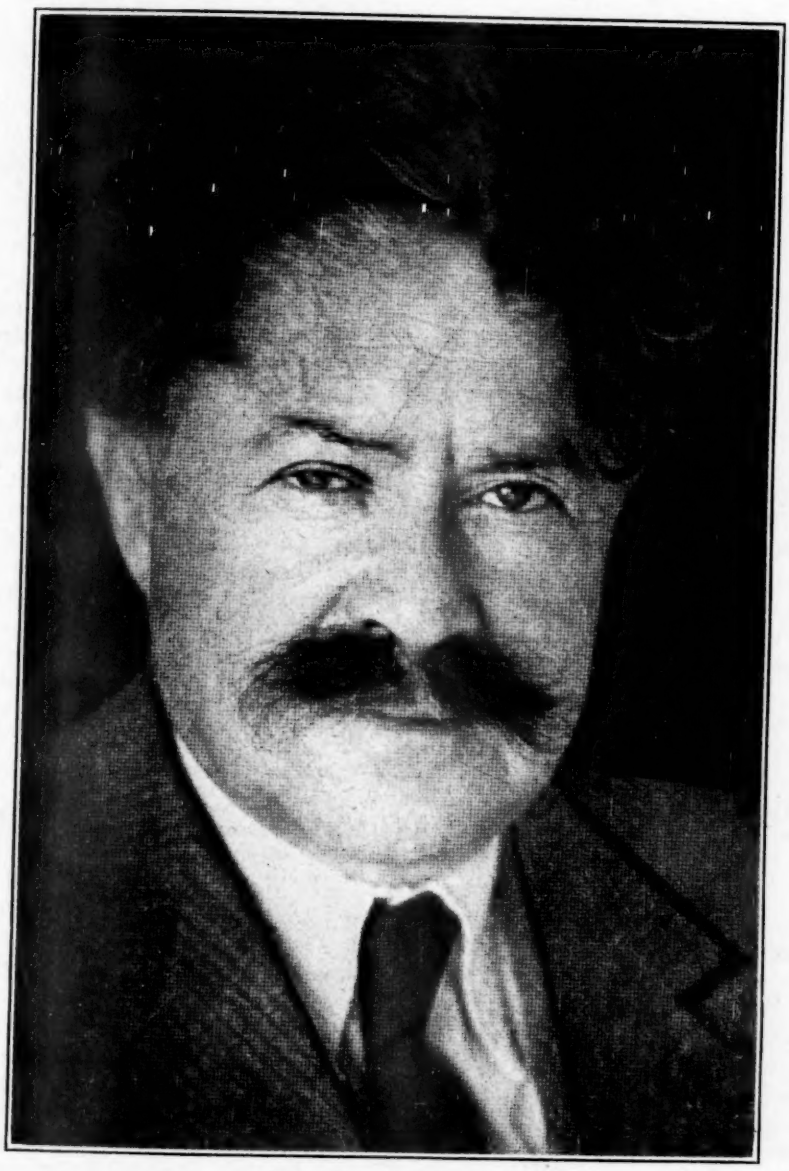
But he was more than a poet whose works were read for mere entertainment. He was his people's physician, so to speak. He tried to give them a new outlook on life and to stimulate and develop their springs of emotion, rather than their intellectual resources. He tried to focus their attention to the stream of life and to attune their ears to the multitude of harmonious vibrations in nature. Turning to the early history of his nation, he tried to arouse their ancient instincts for life. He tapped all sources and channels of many peoples and tongues, wherever beauty and life were found. So he recreated in Hebrew the classics of various nations. In so doing he reversed the process, for he became, by his skill and ability, a poet for all humanity.



SAUL TCHERNICHOVSKY
1875–1943

Let us unfold the story of this doctor and poet. Tchernichovsky was born on August 20, 1875, in Russia, in the village of Michailovka on the Ukrainian border. This is a country that is well known for the severity of its winters and its burning summers — a vast country in which there is nothing mild or temperate, a land where the cold blasts from the Arctic Ocean sweep down over great stretches of land uninterrupted until stopped by some mountain chain. These scenic and atmospheric conditions made an indelible impression on the young poet's mind and mood. They became his inalienable possessions for the rest of his life. As he later wrote in one of his impressive poems,

> Man is but a tiny land — a plot of earth.
> Man is but a model of his place of birth.

He continues to describe how he spun his dreams in the image and model of his native land. For there he met the eternal wanderer — you will never guess his name — why, the Wind! He often carried dark leaden clouds and at times just played wildly in God's open spaces — a frolic in treasures of ice and snow. There he heard the shrieks of the wild eagle.

Such was also his fate, the poet concludes. Like the eagle's call, he was often misunderstood, and like the Wind, he wandered from place to place.

Tchernichovsky's personality and works also reveal dominant hereditary traits. He came of a stock of rugged people, physically strong and intellectually curious. His ancestors participated in Russia's wars and survived various persecutions. His great-grandfather lived long enough to celebrate a second confirmation (Bar Mitzvah), for he lived one hundred and thirteen years. His mother's father, Saul Karp, after whom he was named, was a cultured and widely traveled man. He mastered the French, Italian and Russian languages. He translated Ukrainian folk songs into Hebrew and then sang them in their original melodies. Several members of his family participated in the Caucasian wars. His father was a righteous and observant Jew. His mother was a cultured and sensitive lady. Her sister was one of the first women to matriculate in a Russian university. As a student, she was attracted to the revolutionary movement and was exiled to Siberia. It was this aunt who started to teach Russian to young Saul when he was but five years old. Two years later, his father began to teach him Hebrew through the medium of Russian. It is told that in order to commit the Hebrew alphabet to memory, young Saul made models of the Hebrew letters with dough and baked them. These alphabet cookies were the joy of the young lad. This is extremely symbolic, for during the rest of his life he succeeded in modeling many a literary dessert out of the alphabets and legends of various nations. He was then prepared for the source book of Hebrew literature, — the Bible, — which he mastered in its original tongue, and this became part of his being. He was also introduced to the modern Hebrew writers and poets, such as Mapu, Lebenson, Dolitsky and Manne. At the age of twelve, he wrote his first poem, "Uriah, the Hittite," which he illustrated artistically himself. But nothing was preserved of his juvenilia. He was a profuse reader and he continued to study Russian literature in its original and translated works.

In 1890, Tchernichovsky went to Odessa and entered the Commercial High School. There he came in contact with a group of men of great vitality — men whose culture was universal. They were dreamers, men of vision, who tried to forge a new dawn and a new freedom. They were the early "Lovers of Zion." This circle of friends made a lasting impression on the youthful student. It was while he was in Odessa that his first Hebrew poem, "Bahalomi" ("In My Dream"), came off the press. It appeared in a Hebrew journal, *Ha-Pisgah*, published in Baltimore, Maryland, in 1893.

In 1896, Tchernichovsky was graduated with distinction from that school. During these years he acquired a working knowledge of the English, German and French languages. He had a rare gift for languages. Not only was he able, in a short time, to read and study their literatures in the original, but he was able to utilize these languages in his poetic creations. Thus in 1897 he began his translation of *Hiawatha* by Longfellow, which he rendered in lasting biblical verse.

To be fully prepared for his career of a physician, he had to study Greek and Latin. Here again, he was riding Pegasus on his way to medical school. For in 1896 he started to translate the poems of Anacreon from Greek into Hebrew.

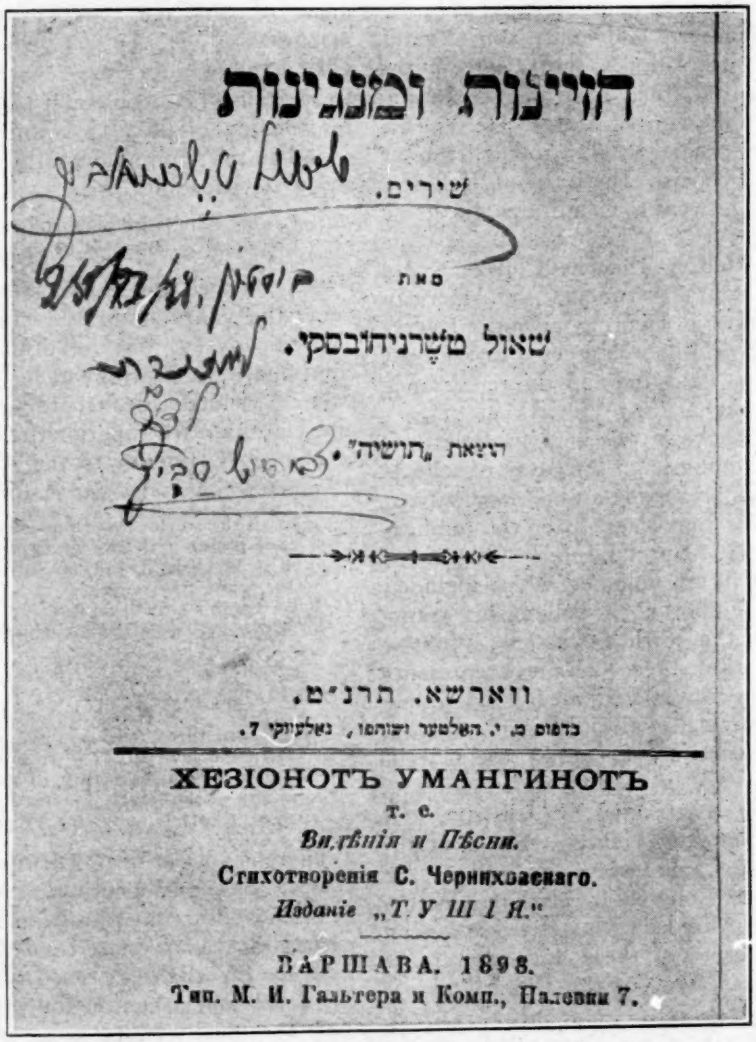
In 1898, Tchernichovsky's first collection of poems was published in Warsaw. It was called Hezionoth Umanginoth (*Visions and Melodies*). At first, most of the critics were harsh and severe. They were dazzled by this poetry's newness. Here was an outburst of feeling, an explosion of strength. Here were new visions, new melodies. Words were used in new combinations and new arrangements. Here was no stream of old quotations, but words to portray certain moods. The critics did not at first grasp the meaning. Were not our own critics dazzled when Walt Whitman first appeared on the American scene? Here, too, was a prophet and poet who exulted in the new strength and life of America. These fountains of poetry do not necessarily follow the old patterns. So it is strange at first. Yet one writer immediately saw this poetry's merit. Reuben Brainin (1862–1939) was the leading Hebrew critic, essayist and biographer, as well as a writer of beautiful lucid Hebrew. In his introduction to Tchernichovsky's first edition, he exclaims: "Here is indeed a poet who is treading a new path. His muse does not appear in borrowed clothes — to be sure, its wings are young and tender, but there are no foreign feathers on them."

In 1899, Tchernichovsky matriculated in the Medical Department of the University of Heidelberg, and spent four years there until 1903. To broaden his general knowledge, he also studied philosophy for the first two years under Professor Kuno Fischer. He also studied the history of religions. Meanwhile he acquired the knowledge of another language — Italian. Although steeped in medical studies, he never forgot his first love — poetry. This is also true of his entire medical career, which he never abandoned. He may have courted Erato (goddess of lyric and love poetry) for a while and then started to flirt with Calliope, but he never abandoned Minerva. There was no jealousy among the goddesses. On the contrary, as we shall see, his medical study influenced his

poetry, while his poetic sensitivity was revealed in his medical practice. So as a student in Heidelberg he published some of his finest poems, among them "Before the Statue of Apollo," "Baruch of Mayence" and "At the Sea."

The next four years, from 1903 on, we find Tchernichovsky in Lausanne, Switzerland, where he received his M.D. degree in 1907. On the completion of his medical studies, he returned to his native land, Russia. For the next three years (1907 to 1910), he served as a physician for the *Zemstvo* (the local town government) in the province of Harkov. There he practiced among the Russian peasants with great success. In 1907, he was arrested in Melitopol, charged with a political offense, but was fortunately released after six weeks of imprisonment. During the next four years he was active in medical work in St. Petersburg, where he served as assistant in the Royal Institute of Medicine.

During World War I, Tchernichovsky enlisted in the Russian army, serving with distinction from 1915 to 1918. Here the poet of love, life and sunshine became the beloved physician of the ill, wounded and maimed. He saw service in a military hospital and received a medal on discharge, as well as other testimonials, including a Hebrew Bible. Many letters of appreciation by soldiers of the White and Red armies were published in the newspapers. After the war he returned to Petrograd, where he served in another military hospital as assistant director of the Department of Sanitation and Statistics for the Red Cross. When the Bolsheviks came into power, he was sent on a special mission to the Crimea. Up to 1922, he was in Odessa as a physician in various military hospitals.


חזיונות ומנגינות

שירים.

מאת

שאול טשרניחובסקי.

הוצאת „תושיה".

וואַרשא. תרנ"ח.

ХЕЗІОНОТЪ УМАНГИНОТЪ

т. е.

Видѣнія и Пѣсни.

Стихотворенія С. Черниховскаго.

Изданіе „Т У Ш І Я."

ВАРШАВА. 1898.

Тип. М. И. Гальтера и Комп., Налевки 7.

An Autographed Title Page of the First Edition of the First Book of Poetry by Tchernichovsky.

That year he went to Berlin, where he lived for several years.

During all these years that Tchernichovsky practiced medicine, he suffered hardships, but his creative activity never ceased. At this time he was engaged in the translation of the *Iliad* and *Odyssey*, as well as in writing many original poems. But not only was he browsing in the world classics: he traveled and visited the lands of many people. In 1925, he visited Palestine and participated in the opening of the Hebrew University on Mount Scopus, where he worked for a short time in the Kupath Holim Hospital, then returning to Berlin. In 1928, he came to the United States. Here he received the honorary degree of Doctor of Hebrew Literature from the Jewish Institute of Religion. In November, 1928, he went to Cambridge, the home of Longfellow whose poems he translated. While here, he visited the Hebrew Teachers College, where American Jewish youths, students at American universities, studied his Hebrew poems. Everywhere in the New World he was greeted as the poet symbolizing the New Palestine and the renaissance of the Hebrew language.

In 1931, Tchernichovsky returned to Palestine, where he became the physician in charge of schools in Tel Aviv. He was also made an honorary citizen of the city. In 1932, forty years after the publication of his first poem, a special Jubilee Committee published his works in ten volumes, which included most of his original efforts, as well as his translations of some of the world's classics. What a luxuriant harvest these ten volumes represent! What a contribution to world literature! Here one finds poetry in practically all its forms — idylls, epics, sonnets, lyrics and dramas, and prose as well. Poetic creations of various peoples and tongues — ancient and modern — attracted his sensitive soul and he rendered them into Hebrew. Songs of ancient Egypt, Babylon and Greece, as well as the works of Shakespeare, Longfellow, Molière, Goethe, Heine, Pushkin and Alfred de Musset, were among his translations. Heroes of these nations were as stimulating to him as some of the Biblical heroes of his own people.

In 1935, as a result of his translations of the Finnish epic *Kalevola*, Tchernichovsky was invited to Helsinki, where he received the award of the Finnish White Rose. Honors were also bestowed on him by the Academy of Athens for his translations of Homer and Plato.

During his stay in Tel Aviv, Tchernichovsky reached the zenith of his productivity. In addition to the continuous flow of his poetical creations, he completed from 1931 to 1933 a Hebrew medical dictionary begun by Dr. Mazia. It is a book of nearly one thousand pages. For each term is given its Latin, English and Hebrew equivalents. Here again, the poet, physician, philologist and scientist found an outlet. Some of the medical terms have a poetical tinge to them. Where he could not find an old term hidden somewhere in the ancient literature, he coined a new one. Hebrew, by the touch of this doctor-poet's hand, became rejuvenated, young, vivacious, expressing every mood, every flower and every precious stone, as well as many new inventions. In reading his poetry, one feels the vitality, frivolity and energy of a living tongue and at the same time the wisdom and judgment of old age, vast experience and ripened maturity.

In many of his poems, Tchernichovsky endeavored to revitalize his people and to arouse in them a will for the joy of life. He wanted his readers to respond to the symphonic harmonies of nature and to enjoy its sunshine.

> For his stare is Life, and Life and Love are One,
> And death's domain is where there is no sun.

Bialik glorified the *Hamathmid* — the diligent student, the guardian of the holy fire, the intellect. Tchernichovsky, on the other hand, stressed the emotional side, bearing out his philosophy, or rather poetical vision of life, according to which the feelings and emotions are superior to the intellect. A sense of beauty is superior to the accumulation of facts, no matter how essential. As he says:

> In all the world, three precious crowns there be,
> Each crown with its own light for men to see,
> Of strength, of Torah, and of beauty are the three.
> Our praise to strength!
> To Torah's crown, no less,
> Of beauty's worth, who shall attempt to guess?*

In another poem, "*Sholosh Amitoth*" ("Three Truths"), he says:

> There are three truths in the world — each truth and its particular glory. The truth of the individual — the truth of strength; the truth of the Torah — the truth of the many — the truth of beauty, the universal truth. Truth of beauty is noble and superior to all.

There is a great deal of truth and realism in these verses. Here is a poetic differential diagnosis of a keen and observant physician. Does not the world witness at the present time the curse of intellect without the slightest sense of beauty? Were not evil forces unleashed on the world by a nation that was technically developed and scientifically informed? Are not the foundations of civilization crumbling because a sense of beauty has given way to technical success?

So the doctor turned to beauty wherever it could be found. This prompted him to say enthusiastically to the statue of Apollo, the symbol of youth, love and life:

> To thee I come, O long-abandoned God
> Of early moons and unremembered days,
> To thee whose reign was in a greener world
> Among a race of men divine with youth,
> Strong generations of the sons of earth.

For this type of poetical utterance, Tchernichovsky was erroneously labeled as the Greek in Hebrew

*Translated by Dr. M. Waxman.

literature. As a matter of fact, it is the Jew in him that speaks in this way — a Jew conscious of his long literary heritage. Was not the poet of the Song of Songs crying for love and life when he said:

> Let him kiss me with the kisses of his mouth —
> For thy love is better than wine.

In truth, Tchernichovsky is a firm believer in the God of the Bible, for he ends this poem by saying:

> I kneel to life, to beauty and to strength,
> I kneel to all the passionate desires
> Which they, the dead-in-life, the bloodless ones,
> The sick, have stifled in the living God,
> The God of wonders of the wilderness,
> The God of gods, who took Canaan with storm
> Before they bound Him in phylacteries.

In Tchernichovsky's rare personality and poetry, three vital elements harmoniously fused and mutually influenced each other. He symbolizes by his religion the Jew of the Biblical period, by his nature a gifted and sensitive modern poet and by his training a keen and observant physician. He is neither Hellenistic in his poetry nor pantheistic in his faith. He was sensitive to beauty everywhere. He would use a Greek theme as a frame to reveal more sharply the ideas of his people. This is clearly revealed in the poem "*Ha-Pesel*" ("The Statue"), dedicated to the students of the Hebrew Gymnasium in Lithuania. He colorfully and artistically describes the pomp and ceremony in a Greek temple at the unveiling of a new statue of the God Zeus. The curtain rises and the entire congregation kneels in great awe. Only one person remains standing — the sculptor of this marvelous statue. For at the moment of the unveiling there appears before him the face of the Lord — that is even more sublime, more beautiful and more divine. Does not this poem reveal the great Jew as well as the great poet? When it comes to the suffering of his people, the doctor, as well as the poet and prophet, comes to light. Tchernichovsky neither weeps nor mourns. There is nothing pusillanimous about his poetry. He is like a great physician who loses his favorite patient and deeply feels the pain and sympathizes with the family, but calmly analyzes the case and goes to his next patient. Having isolated the cause of the illness, Tchernichovsky is encouraged to conquer the malady and wipe it off the earth. Here is where he differs from his predecessor, the immortal Bialik. During the massacre in Russia in 1909, Bialik wrote a poem called "*Be-Ir Ha-Haregah*" ("In the City of Slaughter"). Here he appears as a new Jeremiah, with a modern scroll of lamentation. He proclaims to the world the cruelty of man to man. His descriptions are soul piercing and tear at the fibers of the heart. This poetry conveys the wrath and sorrow that only the poet of a martyred people could describe. It is written in hammered Biblical style, slow moving and weighty rhythm. The poem gives the effect of a memorial hymn played on a gigantic electric organ whose vibrations rise to pierce the skies and to shake the earth at the same time. Bialik is at times despondent.

Tchernichovsky, the physician, is more comforting. He speaks in the style of Isaiah. He, too, feels the sorrow, the pangs of injustice, but the doctor is calm and not despondent. In 1920, during the slaughter of his innocent brethren in the Ukraine, he wrote a poem called "*Zoth Thei Nikmatheinu*" ("This Will Be Our Revenge"). "No one listens to the pangs of the widow, no one comforts the infant, but there is revenge in the world." This revenge is not to come by retaliation — he is too sensitive for that. There shall be no retaliation until the image of God is erased from us, as well as the lines of ancient nobility that are on us. It shall not come as long as we bear the yoke of the Ten Commandments. But remember — these acts of murder will poison the very soul and the very fibers of the tormentors. It will breed more cruelty, more immorality and more demoralization. It will penetrate into the heart of the children and their children's children for generations to come. For the cry of blood must be stilled. Here the doctor looks on evil and cruelty as on deadly poisonous bacteria that produce a bacteriophage that eventually destroys the bacteria that produced it. How prophetic is the doctor's prognosis! Nations that permitted evil forces to victimize innocent peoples are now reaping the fruit of the harvest. Here is poetry to be taught to the world, to be included with other rules of medical hygiene for the soul.

Such is briefly the life and work of the doctor and poet, Tchernichovsky. But to appreciate him fully one must read his poems in their entirety and in the original. He belongs to the golden chain of Hebrew poets and physicians. Dr. Tchernichovsky was not a rare phenomenon in the long history of his people. There is a golden tradition of nearly ten centuries of medical Hebrew poets. Each one, more or less, reflected the period of world history in which he lived. As early as the eleventh century, we find the physician in Cordova, Spain — namely, Judah-Ha-Levi (1085–1142). He was a philosopher and a serene and tender poet whose devotional songs in the spirit of the *Psalms* are included in the synagogical liturgy. He too had a longing for Zion that inspired him to compose a number of beloved poems. He too was buried in Palestine in 1142.

During the Golden Age of Hebrew culture in Spain, we find two other Hebrew medical poets: Judah al-Harizi (1170–1230) and Joseph Zabarra (1140–1200). Both were contemporaries of the great Maimonides. All were heirs to a noble tradition of intellectual activity.

In the thirteenth century there lived in Italy the medical Hebrew poet, Immanuel Ha Romi (1265–1330). He reflected the period of his time and was respected by Jews and Gentiles, especially the

literati of the age. He was a friend of Dante and wrote a fine elegy in Italian after the latter's death. In the eighteenth century flourished the poet Ephraim Luzzatto (1729–1792). He died in London. In the nineteenth century there was Judah Lob Katzenelson (born in Tchernigow in 1847; died in Petrograd in 1917). He was a physician and scholar who wrote poems and sonnets, in both Russian and Hebrew, as well as a Hebrew work on talmudic medicine. Finally comes the minor Hebrew poet and physician, Isaac Kaminer (1836–1901).

* * *

Such is the golden tradition of Hebrew medical poets, among whom Dr. Tchernichovsky was the ultramodern. His muse raised him to new heights in poetry.

Tchernichovsky died of leukemia in the Hadassah Hospital in Tel Aviv on October 14, 1943, the first day of Succoth, the holiday of the harvest. His casket was draped in the talith (the prayer shawl) and the Jewish flag. The pallbearers were professors of the Hebrew University and members of the Jewish Agency. The funeral procession was followed by the children of the schools and by soldiers of the Allied forces stationed in Palestine. The poet was buried near his friend, Bialik.

Tchernichovsky is the most modern Hebrew poet who draws his inspirations from the far past — his roots penetrate deep into the springs that nourished and nurtured the Bible. Like the prophets of old, he also had visions about the future. When his works are rendered by poets into other living tongues, as he rendered the world classics into Hebrew, humanity at large will enjoy its beauty and sunshine, as it does the other sacred writings of his prophets and poets. For Dr. Saul Tchernichovsky had great hopes in the eternal and final victory of man. Mankind may be humiliated at times. "Mobocracy" may unbridle the passions of a populace, and leave the light of civilization a tiny flicker. Yet eventually, our poet believed, the spirit of man will win out.

Laugh, O laugh at all my visions,
For I'm dreaming audibly;
Laugh, for I believe in man still,
For I still believe in thee. . . .
Man shall rise to heights of glory,
Vanity's fetters from him shed,
Till the worker starves no longer,
Spirit freed and hunger fed. . . .
I believe, too, in the future,
Tho' the day's not close at hand;
It will come — then peace and blessing
Will be borne from land to land. . . .
A poet then shall sing a new song.
To beauty exalted then awake;
From my grave, for him, the young one,
They'll pluck flowers, wreaths to make.

483 Beacon Street

MEDICAL PROGRESS

NEW BIOLOGIC CONCEPTS DERIVED FROM RESEARCH ON SULFONAMIDE DRUGS*

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CHEMOTHERAPY has a long history, progressing from the older treatment of syphilis by mercurial inunctions to the successful use of such agents as arsenicals, bismuth and quinine against syphilis, malaria and other parasitic diseases. No chemotherapeutic agent, however, has affected so many lives so soon after its discovery as have sulfanilamide and the related sulfonamide compounds, which have opened the era of chemotherapy of bacterial diseases. Investigations involving these drugs have not been limited to practical therapeutic problems; they have led to a number of fundamental advances in pharmacology and have had ramifications in related scientific fields. The value and the limitations of these drugs in overcoming a variety of infectious diseases are widely recognized; this paper will rather be devoted to a review of the broader biologic implications of the knowledge gained in the ten years in which these compounds have been used.

Several attributes of sulfonamide drugs have contributed to the rapid accumulation of knowledge of their pharmacology. These are chemical simplicity and ease of synthesis, which have permitted rapid development of inexpensive manufacture and widespread use; the possibility of synthesis of a wide variety of derivatives of the original sulfanilamide; effectiveness against susceptible organisms without the aid of the body's natural defenses, permitting in vitro study; dissociation as acids; and the possession of a readily diazotized amino group, which permits accurate and simple colorimetric determina-

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tion of concentrations of the drugs at therapeutic levels.

Distribution of the Drugs in the Body

The absorption, distribution and excretion of these drugs have been studied extensively, since their concentrations are so readily measured. The bacteriostatic action of a given drug is proportional to its concentration in the body rather than to its dosage. It is therefore desirable so to adjust the dosage as to maintain an optimal concentration in the blood, which strikes the proper balance between effectiveness and toxicity. Blood concentrations of 5 to 15 mg. per 100 cc., which are usually sought for the various drugs, are in general maintained by a daily dosage in adults of 4 to 6 gm. There is, however, significant individual variation in the rates of excretion and of acetylation (which renders the drugs nonbacteriostatic). Patients with decreased renal function excrete these drugs more slowly, so that dosage must be watched even more carefully to avoid excessively high concentrations in the body. Smaller, less toxic doses have been recommended for prophylaxis against the recurrence of rheumatic fever[1, 2] and for the treatment of superficial infections of the urinary tract.[3, 4]

The frequent measurement of blood sulfonamide concentration has shown that therapeutic levels are obtained quickly only with a large initial dose followed by small maintenance doses. Because of the time lag of several hours before an orally administered sulfonamide is absorbed sufficiently to afford a therapeutic blood level, it is advisable in patients with fulminating infections, such as lobar pneumonia and meningitis, to administer the initial dose intravenously in the form of the sodium salt. This system of variable dosage might well be of value with other drugs, since the lack of chemical methods of measuring concentrations of most drugs has caused physicians to think traditionally in terms of fixed dosage rather than according to the more significant concept of concentration in the body. There are wide variations in individual tolerance to certain drugs, such as aspirin and colchicine; methods of measuring blood levels might contribute materially to a rational employment of these substances. This approach has recently been successfully applied to the salicylate treatment of rheumatic fever.[5]

The levels of sulfanilamide found in the cerebrospinal fluid are usually almost as high as those present in the blood, whereas the levels of sulfathiazole are only approximately 25 per cent of the blood levels; the ratios of blood to cerebrospinal fluid for sulfapyridine and sulfadiazine are intermediate. At first this was explained by a supposed poor diffusibility of sulfathiazole through the blood-brain barrier, leading to the conclusion that sulfathiazole, although an excellent drug in the treatment of systemic infections, is a poor choice in the treatment of meningitis. This explanation and conclusion was invalidated by the discovery that the sulfonamides are bound in varying degrees to plasma proteins, particularly to albumin.[6, 7] Only 20 per cent of sulfanilamide but 75 per cent of sulfathiazole in plasma is bound. The type of binding noted for sulfonamides is a rapidly reversible equilibrium between protein, bound drug and unbound drug. Since only the unbound drug can permeate into the cerebrospinal fluid, it follows that there is no lack of diffusibility on the part of sulfathiazole. Further, since it is highly probable that only the unbound drug is bacteriostatic,[7] the 1.2 mg. per 100 cc. of sulfathiazole in cerebrospinal fluid, which is essentially protein-free, would be expected to be as effective as the 5 mg. in the corresponding plasma, of which only 1.2 mg. is unbound. This theoretical analysis is supported by numerous clinical observations of the efficacy of the highly bound sulfathiazole and sulfadiazine in the treatment of meningitis. There is now no justification in treating any case of meningitis with the relatively ineffective sulfanilamide. It may also be pointed out that binding to nondiffusible constituents is a mechanism that must be borne in mind in interpreting the distribution of any drugs or other permeable substances between intracellular and extracellular fluids or between two extracellular fluids such as cerebrospinal fluid and plasma.

Mode of Action

It was early observed that the sulfonamides exert little bacteriostatic effect in the presence of pus, meat extract, yeast extract and other biologic mixtures — indeed, they are quite ineffective in the local or systemic treatment of walled-off purulent infections unless the pus can be drained. Woods[8] tested the effect of various chemical reactions on the inhibiting power of yeast juice, and concluded that the inhibiting factor behaves exactly like *p*-aminobenzoic acid. This pure compound was in turn found to be a powerful inhibitor, interfering with the action of sulfanilamide when present in only one five-thousandth of the concentration of the drug. A practical result of this discovery has been the addition of *p*-aminobenzoic acid to the medium used for cultures in cases receiving a sulfonamide, to eliminate the possibility that the drug present may mask the presence of bacteria.[9] A much more important outcome is the theoretical concept of competitive inhibition between sulfonamides and a metabolite, *p*-aminobenzoic acid, essential for the multiplication of the organism.[8] Proof of this concept depends on evidence that *p*-aminobenzoic acid is an essential growth factor for sulfonamide-susceptible bacteria. Diligent search has disclosed very few organisms — and these nonpathogenic — in which *p*-aminobenzoic acid appears to be a growth factor[10, 11]; for the rest it is necessary to assume that the organism synthesizes enough *p*-aminobenzoic acid to meet its normal require-

ments, but not enough to compete with bacteriostatic concentrations of sulfonamide drugs.

It is assumed in analogy to the participation of such vitamins as thiamine and niacin in oxidation-reduction enzyme systems that *p*-aminobenzoic acid is a vital link in some enzymatic mechanism. The sulfonamides on this assumption compete by possessing a chemical configuration that permits them to occupy a position in the enzyme that is ordinarily held by *p*-aminobenzoic acid, but lack the complete configuration necessary for the function of the latter. That *p*-aminobenzoic acid and the sulfonamides may be expected to be attracted to a similar position on an enzyme molecule follows from the extremely similar configurations of their structural formulas. Although the nature of the enzyme concerned is as yet completely unknown, the concept that sulfonamides act by competitive inhibition of an enzyme reaction is widely accepted.*

The bacteriostatic action of sulfonamides does not necessarily occur immediately, for it has been shown with *Escherichia coli* that multiplication takes place for about six cell divisions before it ceases in the presence of adequate concentrations of sulfonamides.[14] The implications of this fact for the mode of action of the drug are not clear; it may possibly be related to the available stores of *p*-aminobenzoic acid. From a practical point of view, this emphasizes the importance of early treatment and may be one reason why overwhelming cases of meningitis or pneumonia are fatal in spite of treatment by a sulfonamide drug to which the organism is susceptible.

Considerable understanding has been gained by studying the bacteriostatic efficacy of a series of compounds derived from sulfanilamide by substitutions in the amide radical. Although the precise values reported for the drugs vary with the organism, medium and particular end point chosen, in vitro studies indicate that, in contrast to the early impressions, there is no specificity of any particular drug for a given organism.[15] In the earlier studies on the physical chemistry of these drugs,[16, 17] it appeared that the bacteriostatic power could be correlated with the extent to which the drug was ionized as an anion at the hydrogen-ion concentration of body fluids or ordinary culture media (pH 7.4). The degree of ionization is conveniently represented by the pK, which is the pH at which the drug is 50 per cent ionized. Thus, at pH 7.4 sulfathiazole (pK 7.1[18]) is largely ionized whereas sulfanilamide (pK 10) is ionized to the extent of only a fraction of 1 per cent and hence must be present in much greater concentration in order to be effective. This explains the excessive disproportion in the concentrations of sulfanilamide and *p*-aminobenzoic acid competing with each other, since the latter is essentially completely ionized at pH 7.4. With recalculation in terms of concentration of anions, *p*-aminobenzoic acid and various sulfonamides compete with each other in similar concentrations.[17]

Further work with new drugs showed this scheme to be an oversimplification, for when drugs were synthesized with pK values even lower than that of sulfathiazole, and consequently were even more completely ionized at pH 7.4 than is sulfathiazole, they were found to be less bacteriostatic.[18] This can be explained by assuming a dependence of bacteriostatic potency on certain physicochemical functions (acidity of the anion[19] or negativity of the sulfone group[18]) that vary with the pK, having a maximum value at about pK 6.8. These theories lead to the prediction that it will be impossible to synthesize a member of this series, working by the same mechanism, that will be more bacteriostatic than are sulfathiazole, sulfadiazine, sulfamerazine and certain other sulfonamides now in widespread clinical use, which have pK's at or close to this maximum. Efforts to improve on the present compounds must, then, be aimed at a reduction of toxicity, or at a change of structure so radical as to introduce a new mode of action.

The binding of sulfonamides to plasma proteins, which was discussed in connection with the problem of distribution in the body, was found to parallel the in vitro bacteriostatic potency of a series of sulfonamide compounds, the drugs with the greatest binding tendency being in general the most bacteriostatic.[20] This correlation suggests that the drugs in their assumed action by competition with *p*-aminobenzoic acid are bound to the hypothetical enzyme by the same forces that bind them to other proteins. Sulfamerazine and sulfamethazine, which have recently been found to be potent drugs, are also highly bound.[21]

Resistant Strains of Organisms

The bacteriostatic action of sulfonamides cannot involve an enzyme system that is universally present and susceptible in bacteria, since these drugs are effective against only a limited number of gram-positive and gram-negative organisms. Furthermore, certain patients have been found to be infected by drug-resistant strains of a number of ordinarily susceptible species of organism, whereas others have strains that become resistant during the course of prolonged exposure to moderate concentrations of the drugs in vitro or in vivo.[22] The study of metabolic differences between resistant and susceptible strains appears to be one of the most attractive methods of probing further into the mode of action of the drugs. Certain sulfonamide-resistant strains of *Staphylococcus aureus* have been reported to synthesize *p*-aminobenzoic acid, which can be detected in the filtrate from the organisms,[23]

*It has been noted that sulfanilamide inhibits the enzyme carbonic anhydrase[12, 13] which is responsible for the rapid conversion of carbonic acid or bicarbonate to free carbon dioxide in the body. This property accounts for the moderately depressed plasma carbon dioxide combining power sometimes noted in patients receiving sulfanilamide, but since the property is not shared by the other drugs in the series, it cannot be concerned in their bacteriostatic action.

but since the method of detecting this acid was biologic rather than chemical, it is not certain that the drug-inhibiting substance elaborated by the organisms was actually *p*-aminobenzoic acid.

In the study of earlier chemotherapeutic agents, it has been difficult to obtain direct evidence of the relation between resistance to treatment and variations in the host and in the infectious agent. With syphilis, indirect evidence indicates that in at least some cases resistance to treatment depends on factors in the host rather than on variations in the strain of the organism.[24] The effectiveness in vitro of sulfonamides has made it possible in many cases of gonorrhea and other diseases to place the responsibility for failure of therapy directly on the organism. With the gonococcus, a simple method has recently been developed for testing in vitro the response to sulfathiazole of each patient's strain of organism.[25] This permits accurate prognosis of the results to be expected from sulfonamide therapy and minimizes the time wasted before recognizing the desirability of other forms of therapy — for example, fever and penicillin — in sulfonamide-resistant cases. As the variety of available chemotherapeutic agents grows larger this principle will undoubtedly find ever-increasing application, especially with serious diseases where the saving of life may depend on early use of an effective drug.

Toxicity

Even the best drugs now available give rise to toxic reactions, reported in as high as 10 to 15 per cent of some series, which are occasionally fatal. A large proportion of the toxic reactions of these drugs (except for the relatively soluble sulfanilamide) are due to the unusually large doses necessary and the low solubility of their acetyl derivatives. These properties, together with the high renal clearance of these compounds,[26, 27] frequently lead to concentrations in the urine in excess of their solubility, with resultant crystallization in the urine. Sufficient crystallization occurs in the tubules or ureters, renal damage results, but it is not clear whether all the toxic effects of sulfonamides on the kidneys arise from such precipitation. With drugs of which the degree of ionization varies significantly in the pH range of the urine — for example, acetyl sulfadiazine — the solubility can be markedly increased by rendering the urine alkaline. This type of toxic reaction can therefore be circumvented with certain drugs by administration of alkali.[28, 29] Urea has also been shown experimentally to inhibit renal precipitation of the drugs.[30]

The other toxic reactions are much less well understood and consist largely of primary toxic effects — for example, nausea, vomiting, headache and mental confusion — and a group of reactions that are usually delayed — hemolytic anemia, agranulocytosis, jaundice and drug fever, with or without a rash. Longcope[31] has recently stressed the similarity of the latter group to serum sickness, pointing out that although clinically these reactions of sulfonamides and other chemical drugs have many characteristics of sensitization phenomena, direct proof by demonstration of antibodies has not been obtained, and most workers have failed to demonstrate skin reactions to the drugs with any regularity. The unpredictability and persistence of these hypersensitive reactions present a contraindication to the use of these drugs in treating relatively trivial infections or in prophylaxis, and therefore limit their utility.

Metabolic Studies

Although it has already been established that certain drugs act by inhibiting enzymatic activity,[32] — for example, physostigmine inhibits choline esterase, — the present concept of the mode of action of sulfonamides by competitive inhibition of an enzyme provides a further thought-provoking link between drugs, vitamins and enzymes. It has already led to two important developments outside the field of chemotherapy. In the first place, *p*-aminobenzoic acid has been found to be an essential dietary factor in rats and chicks,[33, 34] although evidence has been presented that this action may depend on stimulation of certain gastrointestinal micro-organisms to synthesize essential factors.[35] In the second place, competitive inhibition has been shown between other vitamins and structurally similar compounds, which behave as antivitamins. Thus the pyridine derivative of thiamine interferes with the growth of bacteria that require thiamine.[36] Similarly, nicotinamide and the co-enzyme derived from it have been observed to antagonize the effect of various sulfonamides on the growth of *Staph. aureus*,[37, 38] whereas sulfapyridine and sulfathiazole (but not certain other sulfonamides) inhibit the stimulation of the respiration of the dysentery bacillus by nicotinamide or the co-enzyme.[39] The similarity of chemical configuration between nicotinic acid and sulfapyridine may not be an important factor in this antagonism, since the other sulfonamides that exhibit the reaction do not have the pyridine nucleus of these two compounds.

The metabolic effects of the sulfonamide drugs are not confined to bacteria. Evidence of the importance of antivitamins as well as vitamins in animal nutrition has been provided by the observation that sulfapyridine inhibits the curative action of nicotinic acid in dogs suffering from a deficiency of this vitamin.[40, 41]

Sulfaguanidine and sulfasuxidine (succinyl sulfathiazole) are sulfonamide drugs with properties of solubility and absorption that permit high intestinal concentrations along with low concentrations in the body fluids. These drugs have been used in the treatment of certain types of enteric infection and in preoperative prophylaxis of peritoneal infection following gastrointestinal surgery. Besides

this practical utility, the drugs have provided an explanation for apparent differences in the vitamin requirements of various animal species. Whereas the concept of synthesis of vitamins by bacterial flora was first developed in relation to vitamin K, the suppression of such synthesis by these sulfonamide intestinal antiseptics has permitted the demonstration that biotin[42] and folic acid[43, 44] are essential for complete nutrition of the rat's tissues as well as of bacterial and animal species in which they have earlier been proved to be essential. The elimination of intestinal bacterial synthesis may be expected to provide further solutions of problems in vitamin research. The production of leukopenia and anemia in rats by these drugs permits a new experimental approach to the problem of blood dyscrasias.[44]

An entirely new field of chemotherapy, not involving infections, has arisen from the observation that rats receiving huge doses of sulfonamides developed an enlargement of the thyroid gland shown to be due to interference with the response of the gland to the thyrotropic hormone of the anterior pituitary glands.[45, 46] Further investigation of this phenomenon led to the development of other unrelated compounds, thiourea and thiouracil, that have proved useful in the treatment of hyperthyroidism, and that may in the future replace much of the surgical treatment of this disease.[47]

* * *

Besides their great practical utility, the sulfonamide drugs have provided valuable fundamental advances in pharmacology and related fields, which may serve as a pattern for the study of the reactions of other drugs with the host and with the infecting agent. Their distribution in the body is primarily dependent on their degree of binding to plasma albumin, which in turn parallels their bacteriostatic power in its dependence on certain physicochemical functions of the acid-base dissociation constants of various members of the series. The antagonism between sulfonamides and a closely related chemical, *p*-aminobenzoic acid, has led to a theory of the mode of action of these drugs by competitive inhibition of a postulated bacterial enzyme. Para-aminobenzoic acid has subsequently been recognized as a vitamin in the nutrition of certain vertebrates, whereas the concept of competitive inhibition has led to the discovery of other antivitamins. Intestinal antisepsis by sulfonamides has made possible the discovery of new food factors essential in mammalian metabolism. Investigation of a toxic effect of massive sulfonamide therapy in animals has led to the development of other compounds that may significantly modify the treatment of hyperthyroidism.

The broad utility of sulfonamides has developed an unprecedented interest in the field of chemotherapy. It may be partly by virtue of this stimulation that penicillin, which lay relatively unrecognized for ten years following its discovery by Fleming in 1929, has finally been found to surpass the sulfonamides in therapeutic effectiveness and freedom from toxicity. The development of other chemotherapeutic agents of microbial and synthetic origin offers future possibilities that may ultimately extend well beyond the range of infectious diseases.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30241

PRESENTATION OF CASE

A fifty-seven-year-old housewife entered the hospital because of pain in both sides of the abdomen.

The patient had been in apparent good health until two years before entry, when she experienced a knifelike pain in both lower quadrants of the abdomen. The pain caused the patient to double up and remained fairly severe for seven days. It was more marked on the left than on the right, was spasmodically crampy and did not radiate. Within six hours of the onset of illness, she developed nausea and vomited greenish material, without any gross blood, coffee-grounds or fecal material or recognizable food. The vomiting was followed by "watery diarrhea" in which no blood or mucus was apparent. She had no chills or fever. She was seen by her physician, who prescribed pills and bed rest. The symptoms disappeared in about two weeks, and she felt "fine" during the ensuing seventeen months.

Seven months before entry she had recurrence of the pain in the lower abdomen. This time, however, the pain was dull, not crampy, and of much less intensity according to one story, but crampy and knifelike by another. It involved both lower quadrants, but was a little more pronounced on the left than on the right, and radiated to the vagina and to both flanks. She vomited greenish material and had diarrhea productive of bright red blood and mucus. This apparently lasted for several hours, but these attacks recurred on the average of once a month, continuing one or two days but without blood in the stools. Between the attacks she felt weak and had a poor appetite. During the last month before entry, the pain became almost constant and there were bouts of diarrhea, the last episode occurring two days before admission. She had lost 30 pounds in six months. There had been no disturbance of urination.

She had had an appendectomy and a bilateral oöphorectomy twenty-four years before admission.

Physical examination showed a well-developed, obese woman in no discomfort. The heart and lungs were normal. There were a sense of resistance and an indefinite mass in the suprapubic region. Rectal and pelvic examinations were negative.

The blood pressure was 130 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 2,850,000, with 65 per cent hemoglobin. The white-cell count was 6900, with 74 per cent neutrophils. The urine was negative. One stool examination was guaiac negative. The nonprotein nitrogen was 25 mg. per 100 cc., and the protein 6.1 gm.; the blood chloride was 109 milliequiv. per liter. A blood Hinton test was negative. Proctoscopic examination was unsatisfactory in that the proctoscope could not be passed into the sigmoid, but so far as could be seen the mucosa was normal. A barium enema showed a pressure defect on the medial aspect of the cecum, which was thought to be due to an extrinsic mass. The terminal ileum could not be filled. The cecum was quite spastic, and could not be filled satisfactorily. A gastrointestinal series was unsatisfactory because of technical difficulties. Fluoroscopically, the esophagus, stomach and duodenum were negative. The motor meal passed easily to the lower ileum and proximal colon. Several loops of the ileum were slightly dilated. The terminal 10 cm. appeared definitely narrow, and the mucosal pattern was not visible (Fig. 1). There was some swelling of the ileocecal valve, and a definite constant deformity of the cecum. A repeat barium enema showed ready filling of the colon. The cecum was spastic, but no constant defect or evidence of pressure on the cecum was seen. No barium entered the terminal ileum. An intravenous pyelogram was negative.

Following admission the patient had vomiting and pain in the lower abdomen for a day or two, but these disappeared. On the eleventh hospital day barium was introduced through the Miller–Abbott tube, which showed a lesion in the terminal ileum

*On leave of absence.

and cecum. No definite shelf could be seen. The mucosal pattern was partially preserved, and there was some swelling of the ileocecal valve. She was given several transfusions, and on the fifteenth hospital day an abdominal exploration was performed.

Differential Diagnosis

Dr. Horace K. Sowles: Apparently from the story the cramps two years before entry were of a mechanical nature. The recurrent pain in the lower abdomen was of the spasmodic type, and there was no fever. Seven months before entry she had a recurrence of these attacks.

The laboratory findings on entry were normal, with the exception of the red-cell count and hemoglobin, which showed a definite anemia. The physical examination was noncontributory. The barium enema, however, revealed a definite lesion. On one occasion the x-ray examination showed something at the cecum that may have been extrinsic, although that was not confirmed on the second examination. The second observation seems to have shown a lesion in the terminal ileum. This could have accounted for her type of symptoms, because she might have had temporary obstruction or partial intussusception at the ileocecal valve, which caused the attacks of pain and vomiting and also, on one occasion, blood in the stools.

The lesions of the terminal ileum are not many. There was apparently no evidence in the x-ray films to suggest regional ileitis, tuberculosis or ulcerative colitis. Perhaps it was a tumor of the terminal ileum, such as a sarcoma or carcinoma. They are rare, but they do occur. A small tumor in the terminal ileum can easily cause intussusception, which would explain the pain but not the severe secondary anemia. One does not usually see a marked anemia like this with lesions of the terminal ileum. It does, however, occur with carcinoma of the cecum; but the x-ray report says that the cecum was normal.

The patient had a secondary anemia and a marked weight loss, so my first guess is malignant disease of the ileocecal valve, and my second choice, regional ileitis, which does not explain the loss of

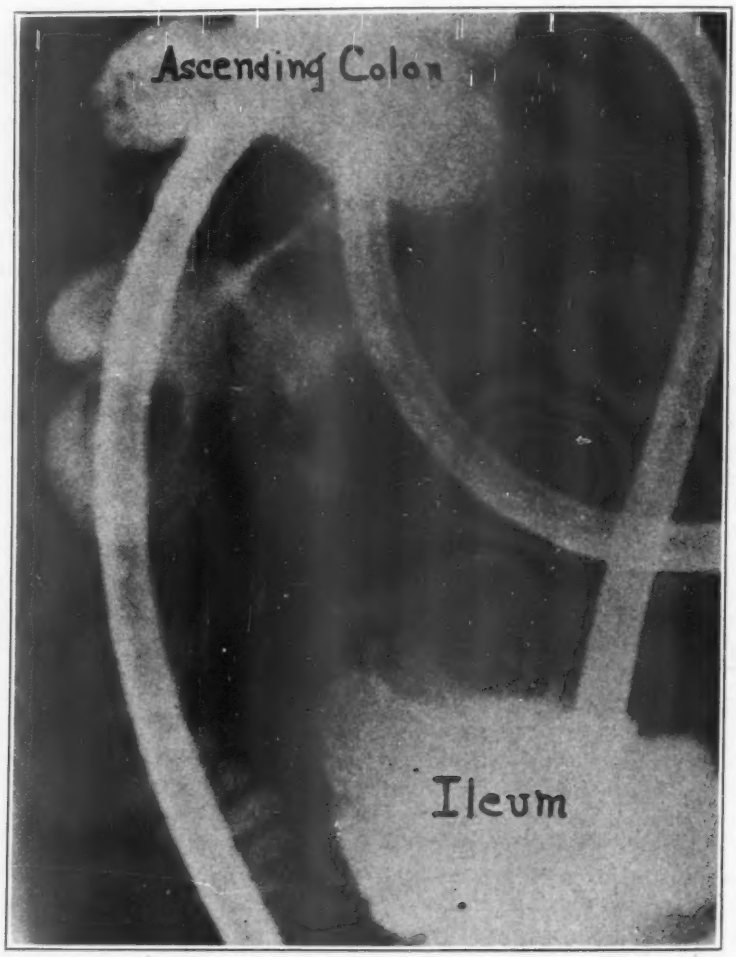

Figure 1. *Spot Film of the Ileocecal Region Showing the Lesion at the Terminal Ileum.*

weight and the anemia so well as carcinoma. Tuberculosis is unlikely. I do not believe that it could have been anything in the pelvis.

In passing, the commonest extrinsic mass around the cecum is an appendiceal abscess, which is not possible in this case because of the previous appendectomy. Furthermore, there is nothing in the history that suggests it.

Dr. Benjamin Castleman: Would you like to look at the x-ray films?

Dr. Sowles: Yes; perhaps the roentgenologist can tell me something that will change my opinion.

Anatomical Diagnosis

Malignant carcinoid of ileum, with metastases to regional lymph nodes.

Pathological Discussion

Dr. Castleman: The clinician in charge of the patient leaned, I believe, toward regional ileitis rather than tumor. At operation the surgeon felt a mass in the region of the terminal ileum and resected the terminal ileum, the cecum and part of the ascending colon. The terminal ileum was markedly dilated. Just proximal to the ileocecal valve, there was a 3-cm. mound-like tan lesion, composed of nodules that were covered with a thin layer of mucosa (Fig. 2). These nodules extended on to the edematous tip of the valve, which protruded into the cecum for about 3 cm. On cross section some of the nodules extended through the muscularis into the serosa.

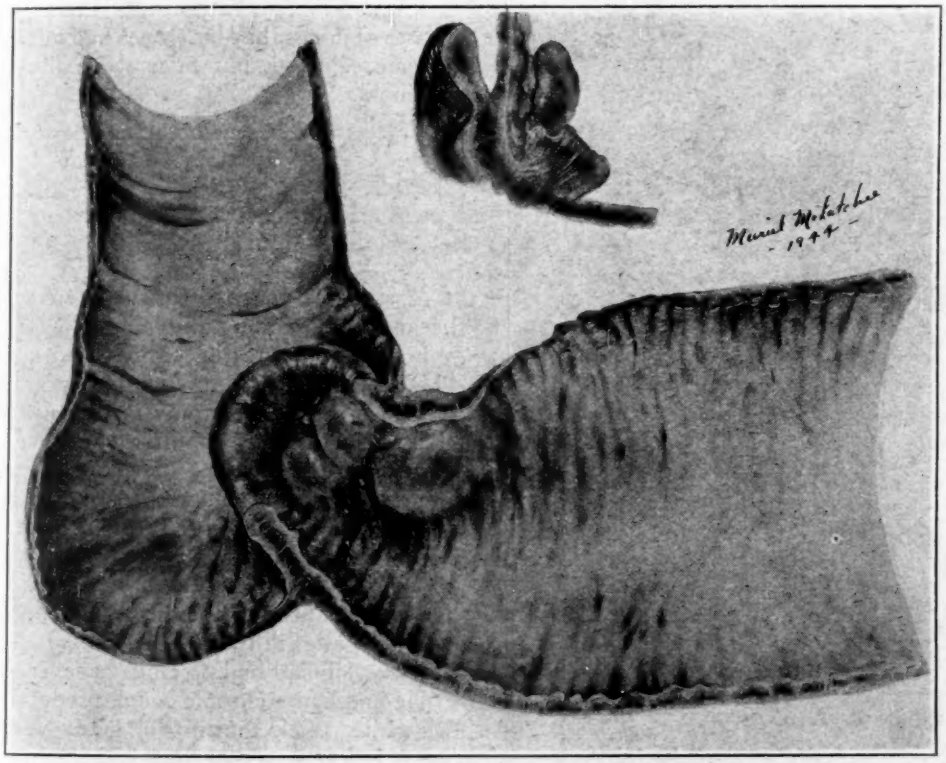

Figure 2. *Drawing Showing the Lesion in the Terminal Ileum.*
The insert represents a cross section of the tumor, with neoplastic tissue above and below the muscularis.

Dr. Milford Schulz: These films demonstrate a lesion in the terminal ileum. The persistent irregularity of the cecum looks more like spasm than infiltration. The mucosal pattern in the terminal ileum is somewhat altered.

Dr. Sowles: If the lesion was a carcinoma, it probably arose in the ileocecal valve, the thickening of the terminal ileum being due to edema. Such lesions are not, as a rule, primary in the ileum.

Clinical Diagnosis

Regional ileitis.

Dr. Sowles's Diagnosis

Tumor at ileocecal valve, probably carcinoma.

At this point, would you like to commit yourself further, Dr. Sowles?

Dr. Sowles: My idea that the pain was due to partial intussusception is proved by the findings. Of course, the commonest cause of intussusception, except in small children, is a tumor of the bowel wall, which is a nucleus for the intussusception. I suppose that it could have been a lymphoma, but

I should think that, because of the marked anemia, she must have had malignant disease of the carcinomatous type.

DR. CASTLEMAN: The tumor involved the entire mucosa, submucosa and muscularis, extended into the serosa and was also present in the adjacent lymph nodes (Fig. 3). All the tumor cells were uniform in size, perfectly round and grouped in masses. The appearance is characteristic of a carcinoid or argentaffinoma — a tumor that arises from the argentaffin cells of the small intestine. These tumors are usually benign, but in perhaps

FIGURE 3. *Photomicrograph of a Metastatic Lesion in a Regional Lymph Node.*
Note the characteristic carcinoid cells.

less than half the cases they metastasize to the regional nodes, where the cells may remain for years without going any farther. They are not uncommon incidental autopsy findings if they are hunted for. The tumors invade the mucosa, but ulceration rarely occurs.

The involvement of the lymphatics in the wall of the bowel and of the regional nodes makes this case a malignant carcinoid. In addition, at operation the surgeon felt a mass in the liver, so it had apparently gone farther than the regional nodes. We have had in the past, I believe, two or three other cases in which the tumor had metastasized farther than the regional lymph nodes, but it is extremely rare. I should think that, even though the patient had a mass in the liver, the prognosis is good for a number of years. These tumors grow extremely slowly. I recall a patient on whom the late Dr. Daniel F. Jones operated for small-bowel obstruction, finding a tumor with a large adherent mesenteric mass of metastases. He resected the small bowel, but left the metastases. This was in 1913, before these tumors were separated from carcinomas, although Dr. J. Homer Wright in his surgical report said, "The arrangement and appearance of these cells suggest the type of cancer that is found in the appendix." The man died twenty years later at this hospital following a prostatic operation, and at autopsy there were the same masses of nodes that Dr. Jones had left in. Some had become calcified, but microscopically they showed carcinoid.

CASE 30242

PRESENTATION OF CASE

A sixty-six-year-old man entered the hospital because of "bladder trouble."

For many years the patient had a great deal of "bladder trouble." About fifteen years before entry he had a left nephrectomy for "pus in the kidney." Following this, his condition improved for a year or two, but then he developed frequency and urgency of urination, with pain and burning. He had aches and pains in the region of the right kidney. About four or five weeks before entry, following a prostatic massage by his physician, he experienced increasing burning, frequency and urgency. There was no change in the urinary stream. The urine was cloudy. He had had no chills or fever.

He had had a chronic cough productive of yellowish-white, thick sputum for many years. For four years before entry he had had shortness of breath on exertion and orthopnea. About seven months before entry he developed ankle edema and "fluid in the lungs." He was put on 1½ gr. of digitalis daily, but the time was reduced to every other day because of an episode of nausea and vomiting. Dyspnea on exertion continued. About two weeks before admission he was seen in the Emergency Ward because of urinary difficulty.

Examination showed considerable difficulty on breathing, with prolonged expiration. The chest was emphysematous. The lungs were full of coarse wheezes. There was tenderness over the bladder. Rectal examination revealed a small nontender prostate, but the base of the bladder and the surrounding areas were exquisitely tender.

The blood pressure was 115 systolic, 70 diastolic. The temperature was 98°F., the pulse 80, and the respirations 30.

The urine was cloudy, with a pH of 6, a specific gravity of 1.010, and a ++ test for albumin. The

sediment contained numerous white cells and occasional red cells.

The patient was given hot sitz baths, demerol and sandalwood oil. He was also given 10 drops of a saturated solution of potassium iodide three times a day, 3¾ gr. of aminophyllin four times a day by mouth and 1½ gr. of digitalis daily. Following this, the dyspnea and orthopnea disappeared. Although there was some relief of urinary trouble, he was still in considerable discomfort because of pain and burning on urination. Two days before admission to the ward he developed "an asymptomatic morbilliform and acneform rash over the entire body and a conjunctivitis." He had had no chills or fever.

Examination on admission showed a patient who looked sick and complained of pain in the bladder. He was not dyspneic. There was a diffuse morbilliform and acneform rash over the face, neck, arms and trunk. Moderate conjunctivitis and a yellow discharge were seen in both eyes. The pupils were small and fixed. Some moist rales and intermittent rhonchi were heard in both bases. The chest was emphysematous. The heart was of normal size. The sounds were distant, and a slight systolic murmur was heard over the precordium. A tender mass, measuring 6 by 7 cm., was palpated in the right flank that seemed to have some connection with the liver and that was finally believed to be a Riedel lobe of the liver. The edge of the liver extended 4 cm. below the costal margin and was tender. There was exquisite tenderness over the prostate and bladder.

The blood pressure was 90 systolic, 40 diastolic. The temperature was 102°F., the pulse 120, and the respirations 30.

Examination of the blood showed a red-cell count of 5,700,000, with 18 gm. of hemoglobin. The white-cell count was 15,300, with 72 per cent neutrophils. The urine contained many white cells and gave a +++ test for albumin.

Potassium iodide was stopped. He was given 2 cc. of Cedilanid intravenously, followed by 100 cc. of aminophyllin intravenously. The skin rash disappeared in twenty-four hours, but the patient's general condition seemed worse. The lungs showed many moist rales. He developed fecal and urinary incontinence and became unresponsive. The nonprotein nitrogen was 60 mg. per 100 cc. He was given intravenous fluids and 1.25 gm. of sulfadiazine intravenously. A Foley catheter was placed in situ. He became anuric, developed marked abdominal distention and Kussmaul breathing, and died on the third hospital day.

Differential Diagnosis

Dr. Fletcher H. Colby: Here is a patient with a long story of bladder trouble. First of all, I think it is reasonable to exclude malignant disease because of the long duration of the symptoms. The outstanding complaint was bladder irritability. In addition to this the patient had some sort of chronic disease, with emphysema or possibly bronchiectasis, which perhaps put a severe load on his heart, so that he had a certain amount of cardiac difficulty. In all probability that is aside from the main issue — the bladder trouble.

The patient went to the Emergency Ward two weeks before he entered the hospital, complaining of his bladder. When he entered the hospital his chief difficulty concerned the bladder. What are the things that may give long-continued bladder irritability? First of all are the local conditions, infection, residual urine from some obstruction to the free flow of the urine and complete emptying of the bladder, such as stricture or enlarged prostate. These seem to have been eliminated because there had been no change in his ability to void. A vesical calculus may cause irritability and infection. Diverticulum of the bladder with infection may also cause considerable irritability of the bladder. This man, however, had had sufficient local symptoms, with tenderness on pressure over the bladder, to suggest even a pericystitis, involvement of the perivesical tissues, in addition to possible local lesions in the bladder, causing marked, continued, chronic irritability.

There is also the upper urinary tract to be considered, and it is reasonable to look there seriously for the source of the trouble. It is quite obvious that infection of some sort played a major role in this patient's illness. We have no x-ray films, which would be helpful, but we have to get along with the information given to us. He had had a nephrectomy years ago, and at the time of entry probably had involvement of the remaining kidney. The 6-by-7-cm. mass felt in the right upper quadrant was possibly the right kidney rather than the right lobe of the liver.

The conditions that may involve both kidneys are not many. In the first place there are the various congenital abnormalities that result in inadequate drainage of the kidney, such as aberrant vessels and kinks and so forth in the ureters, with hydronephrosis. The kidney that had been removed was said to be a "pus kidney." He might have had the left kidney taken out for a calculous pyonephrosis, and on entry he might have had stones and infection on the other side. Pyelonephritis does not sound reasonable. Any of these conditions may cause long-standing bladder irritability, and almost any one of them can be associated with perirenal infection, which may not be evident on examination. The most obvious lesion, however, to account for long-continued bladder irritability, the involvement of one kidney, with removal, and finally the involvement of the other kidney, is renal tuberculosis. Renal tuberculosis may stay dormant in one kidney for a good many years. I saw a patient at the Lakeville State Sanatorium who, after having had one kidney removed for tuberculosis, was well for

thirty-five years, when the other kidney was found involved by the disease. We know that renal tuberculosis can be of long duration and that it is apt to affect both kidneys. Although there is no laboratory evidence, except an acid urine full of pus, to support the diagnosis, I think that the most reasonable diagnosis is renal tuberculosis. I should not be at all surprised if the patient also had tuberculosis in the chest and possibly in other parts of the body.

DR. BENJAMIN CASTLEMAN: Through some error, the clinical abstract of this case was also sent to Dr. Chapman, who was scheduled to discuss another case. It might be interesting to call on him to see if he has any additional remarks to make, or whether he came to the same conclusion as Dr. Colby has.

DR. EARLE M. CHAPMAN: I shall not go into the detailed discussion that I had planned, but I shall make a few remarks from the medical side.

I agree with Dr. Colby in his final conclusion. I thought the patient had tuberculosis of the kidney, but was impressed with the probability that he had more pulmonary tuberculosis than one could detect from the record. An interesting feature is that the disease simulated heart failure, with shortness of breath; in fact, he had been treated for heart failure, having received digitalis and bed rest, but the dyspnea and orthopnea increased. Probably at the final entry he did have heart failure. He did not respond to aminophyllin or digitalis, and potassium iodide caused apparent toxic irritation. That sort of picture can simulate heart failure. It might be labeled a pulmonocardiac picture. The patient had emphysema, and yet all the evidence is against heart disease, because the heart was normal in size; the blood pressure was normal (115 systolic, 70 diastolic) before he went into collapse. The red-cell count was 5,700,000 and the hemoglobin 18 gm., which was a compensatory mechanism for the red cells in the lung circuit to make up for the emphysema. This was not a true polycythemia.

Coming back to the tender mass, I think it was a hypertrophied kidney diseased with tuberculosis.

DR. COLBY: Dr. Butler has just whispered an important differential factor. Pyogenic infection of the upper urinary tract or of the bladder itself, such as an infected diverticulum, usually does not cause such protracted and distressing bladder symptoms and such tenderness as does tuberculosis.

DR. ALLAN M. BUTLER: The bladder irritation in the presence of long-continued renal infection is the thing that places the emphasis on this being tuberculosis.

DR. JOSEPH C. AUB: I saw this man in the Emergency Ward, and I thought that the mass was a big liver. Secondly, the severe pain was in the prostate and around it rather than in the bladder, and I assumed that he had prostatic abscess, which might have ruptured. He had an infection and was in uremia. I thought that he had pyelonephritis from infection around the prostate — an ascending infection.

DR. COLBY: The prostate was described as being small and nontender.

DR. AUB: I disagreed with that.

DR. PAULO ALBUQUERQUE: I saw this patient with Dr. Aub and thought that the pain was in the bladder rather than in the prostate itself. He had some suprapubic pain, which tends to confirm the suggestion of pericystitis made by Dr. Colby and is also consistent with the long-standing bladder symptoms. I also thought of renal tuberculosis in the remaining kidney.

CLINICAL DIAGNOSIS

Prostatic abscess.
Pyelonephritis?

DR. COLBY'S DIAGNOSIS

Renal tuberculosis.

ANATOMICAL DIAGNOSES

Tuberculosis of kidney and prostate.
Cystitis, acute and chronic.
Pulmonary tuberculosis, healed, apical, bilateral.
Pulmonary emphysema.
Bronchiectasis, slight.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The remaining kidney was not particularly large. The upper pole was sclerotic; the lower pole was smooth and somewhat enlarged and, on section, proved to have several reddish-yellow caseous areas. It was suspicious of tuberculosis, but we were not sure at the time of autopsy. The prostate had several small greenish-black abscesses without gross evidence of caseation, such as was present in the kidney. Microscopic sections, however, showed tuberculosis in both the prostate and the kidney. Sections from the bladder, which in the gross was markedly injected and trabeculated, showed no evidence of tuberculosis. The lungs showed healed tuberculosis at the apices, without any evidence of activity. There was a fair amount of emphysema, and in one lower lobe some bronchiectasis.

DR. CHAPMAN: How much bronchiectasis?

DR. CASTLEMAN: Very slight. There was some edema and congestion of the lungs, but no evidence of pneumonia.

DR. AUB: How about the liver?

DR. CASTLEMAN: It was enlarged, and showed marked fatty change. The big mass that was felt was undoubtedly the liver and not the kidney.

DR. JAMES M. NEIL: What did the heart show?

DR. CASTLEMAN: It was normal.

DR. CHAPMAN: You think that the patient died primarily of uremia?

DR. CASTLEMAN: Probably.

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"FOOD FIGHTS FOR FREEDOM"

"Food," according to an alliterative slogan currently popularized by our federal nutritionists, "fights for freedom." We are reminded of the similar cliché of twenty-six years ago, "Food will win the war." The new slogan, as compared with the old, does not represent any particularly original idea, but neither does the fundamental principle on which it is based; when the producers of food leave their plows in the furrows and take up their muskets, food becomes a peculiarly precious commodity. That which is almost taken for granted by a large proportion of the population in a still fertile country in times of peace becomes another weapon with which to fight when the country goes to war.

This sudden relative scarcity of life's indispensable fuel brings into an embarrassing limelight certain interesting jugglings with the nation's food supply that are too easily overlooked in normal times when everyone, like the king in Milne's whimsical verse, had a little bit of butter for his bread. Many of our readers will no doubt recall the chapter and verse:

> The Dairymaid
> She curtsied,
> And went and told
> The Alderney:
> "Don't forget the butter for
> The Royal slice of bread."
> The Alderney
> Said sleepily:
> "You'd better tell
> His Majesty
> That many people nowadays
> Like marmalade
> Instead."

Times, however, can change. Many people nowadays are being reminded by new governmental agencies, different from those that had helped to suppress it, that oleomargarine fortified with vitamin A is a food the equal in every respect, except perhaps for certain esthetic values, of natural (if sometimes artificially colored) dairy butter. Oleomargarine, moreover, if accepted on the basis of its cost of production, should sell for half the price of butter; an ideal food for the low-income groups in normal times — satisfactory for anyone in difficult times.

Here enters pressure politics, one of the black spots of our democratic system, for in practically every state of the Union where margarine competed seriously with the sale of butter, as well as in the Congress of the United States, laws have been enacted to nullify the economic laws of such free competition. Thus, the Bureau of Internal Revenue is authorized to levy an excise tax on every merchant selling the product, and every state has added one or another type of restrictive legislation, such as taxes ranging from 5 to 15 cents a pound, license fees for manufacturers and vendors and, in some instances, special licenses for restaurants and hotels serving margarine to their patrons.

It was only recently, indeed, that the embattled farmers of Wisconsin rose in their wrath against a scientific investigator in their tax-supported uni-

versity who had dared to make public his findings in favor of margarine as a food substance! Thus does an entrenched interest show that sometimes food can fight against freedom.

ARTHROPOD CONTROL

ARTHROPODS such as bedbugs, ticks, mosquitoes and house, stable and deer flies are well known as pests by civilians in this country, and the role played by certain species of anthropods, such as ticks, mites and biting insects, in the transmission of disease is well appreciated by the medical profession. Previous to the present war, the development of insecticides and newer methods of controlling arthropod vectors of disease was being investigated on a smaller scale than was deserved by the immensity and importance of the problem for the protection and betterment of the public health. The present war, with its widespread outposts and fighting throughout tropical and subtropical areas, brought to the fore the urgent need for better and more effective methods of arthropod control, if major and possible disastrous epidemics of certain parasitic, rickettsial, bacterial and virus diseases were to be prevented.

The challenge of the emergency was accepted by the combined intelligence and efforts of medical officers, entomologists, chemists and sanitary engineers. The foresight of this method of attack is now beginning to show successful results. Obviously much of the experimental evidence and procedures developed in the laboratory and the field will have to remain unknown until the end of the war. Certain of the newer developments for arthropod control, however, are reflected in published accounts, particularly those concerning the control of mosquitoes that transmit malaria.[1, 2]

Russell[2] has reviewed the various methods of controlling mosquitoes now in use among the a med forces, methods that he had a great share in developing and applying in the Philippines and India. The measures for military malaria control are applicable both to fixed installations, such as camps, and to field operations. In addition to the well-known methods of controlling mosquitoes by screening, the destruction of larvae and the use of sleeping nets, methods for the spray killing of adult mosquitoes and keeping them away with repellents are now effective.

Methods for the spray killing of adult mosquitoes were given an effective trial in Africa by De Meillon[3] and Ross.[4] Since that time they have been widely used in India,[5] and have been extremely successful in reducing the transmission of malaria.[5] The spray for the disposal of the effective agent, extract of pyrethrum flowers, may be applied with small household spray guns and paint-gun sprayer assemblies or from pressure cans or cylinders. Application in the form of an aerosol from pressure cylinders is becoming increasingly useful both in the field and for effective spraying of aeroplanes arriving from tropical areas. Effectiveness against the tsetse fly,[6] the vector of sleeping sickness, is particularly fortunate because of the great danger of introducing this insect to South America in much the same way as the highly efficient malaria vector, *Anopheles gambiae*, was introduced some years ago in Brazil.

The pyrethrum sprays are contact poisons, killing all species of mosquitoes and certain other insects by a destructive action on the central nervous system. These sprays are nontoxic to man and lower animals, although some irritation and inflammation may be caused by direct contact on the skin.

Mention should a!so be made of mosquito repellents, which are said to be effective for at least four hours. Two of these listed by Russell[2] are known as "612" (Everready) and dimethylphthalate (Skat).

Just how soon some of the above compounds will be released for civilian use will depend no doubt on the length of the war. It should be appreciated, however, that the war has stimulated research in a field that needed development, thereby helping in more efficient control of arthropod-borne diseases and also providing the civilian with an eventual means of alleviating suffering from the bites of the ubiquitous mosquito.

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MASSACHUSETTS MEDICAL SOCIETY

AWARD FOR VALOR

Major John W. Henderson, M.C., A.U.S., of Worcester, was recently awarded the Silver Star for gallantry in action near Alimena, Sicily, on July 22, 1943. The citation reads: "Besieging enemy forces had forced our troops to withdraw. Under cover of darkness, he successfully led a searching party well forward of the outposts to locate and evacuate casualties. His outstanding courage and coolness under heavy enemy fire merit the highest praise."

CORRESPONDENCE

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held on April 12 the Board voted to revoke the license of Dr. Matthias V. Bridges, 41 Buckingham Road, North Andover, Massachusetts, to practice medicine in the Commonwealth because of his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the registration to practice medicine in this Commonwealth of Dr. Ray D. Hester, West Warren, Massachusetts, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Lizzie Osgood, 42 North Street, Pittsfield, Massachusetts, because of a mental condition.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine of Dr. Ralph Coleman, 174 Central Street, Lowell, Massachusetts, because of gross misconduct in the practice of his profession.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. Harry Weintraub, 327 Salem Avenue, Malden, because of gross misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held May 17, the Board voted to revoke the license to practice medicine in this Commonwealth of Dr. William D. Ducy of Brockton, because of gross professional misconduct in the practice of his profession as shown by his conviction in court.

H. QUIMBY GALLUPE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

The first meeting of the year of the New England Pathological Society was held in the Amphitheater of the Mallory Institute of Pathology on Thursday evening, January 20.

The first paper was given by Dr. Maxwell Finland, the title being "Clinical and Physiologic Aspects of Conflagration Injuries of the Lungs and Air Passages." Respiratory complications of conflagration injuries, as judged from clinical observations in the cases from the Cocoanut Grove disaster, vary markedly in severity. The mildest cases may show nothing more than slight cough and irritation of the throat. The next grade of severity is manifested by laryngitis without evidence of pulmonary damage. Then there may be laryngotracheobronchitis, as evidenced by hoarseness, cough, sputum and scattered musical rales. Pulmonary involvement of varying extent is manifested by these signs and, in addition, by increasing numbers of rales scattered throughout the lungs and, later, by atelectasis of varying extent and by signs of small areas of consolidation. The severer cases have more extensive rales with proportionally greater degrees of dyspnea and cyanosis. In such cases, there usually is considerable stridor, which may be severe enough to necessitate tracheotomy or bronchoscopic suction of the larynx and trachea. Such suction is productive of thick mucoid material that may contain fibrinous membranelike structures of varying size. The aspirated material also contains ciliated epithelial cells and many carbon particles.

Practically all cases with injuries to the respiratory tract also have burns of the face and nose. In general, the severity of the respiratory damage is correlated fairly closely with the extent and severity of the surface burns. In those cases from the Cocoanut Grove fire in which there was a great discrepancy between the extent of the surface burn and the severity of the respiratory damage, a story of some attenuating circumstance was usually discovered to account for discrepancy. For instance, some patients with extensive surface burns had covered their faces and noses with wet cloths and had avoided respiratory injury in that way; whereas those who were well clothed, or were stampeded and found themselves beneath other people, had extensive respiratory damage without surface burns.

No single cause of the respiratory injury could be determined. All the patients with the severest pulmonary damage had apparently had prolonged exposure after having become unconscious within the burning building, the loss of consciousness probably being due to excessive amounts of carbon monoxide. In this state the patients presumably inhaled hot noxious fumes that contained products of incomplete combustion of organic materials containing carbon and nitrogen. Some of these products are known to be pulmonary irritants. Interestingly enough large volumes of plasma, physiologic saline solution and other fluids were given to almost all the patients who had severe respiratory damage without apparently producing or increasing pulmonary edema to any appreciable extent. These studies were carried out with the collaboration of Dr. C. S. Davidson, of the Thorndike Memorial Laboratory, and Dr. Stanley Levenson, resident surgeon to the Burn Assignment of the Surgical Services, Boston City Hospital.

In the discussion that followed, the question of the clinical effect of nitrous oxide was raised. If this had been present, in Dr. Finland's opinion, the findings would have been similar to those seen in the Cleveland disaster, in which the patients exhibited more upper respiratory symptoms than those referable to the tracheobronchial tree.

The next paper was entitled "Pathology of Conflagration Injuries to the Respiratory Tract" and was given by Dr. Timothy Leary. He reported the findings in 20 autopsies on Cocoanut Grove victims performed by members of the Pathological Department of the Boston City

Hospital and of the Medical Examiner Service of Suffolk County at the Mallory Institute of Pathology. According to the studies of Mr. Frank Stratton and Dr. W. W. E. Jetter, the blood from 9 of 10 victims dying at the club revealed a saturation with carbon monoxide adequate to account for the deaths. In 6 victims who died at the club there was injection of the mucosa of the upper tract with punctate hemorrhages, as well as hemorrhagic edema of the widely distended lungs.

Among the hospitalized victims the outstanding symptoms were respiratory and were responsible for the high mortality. The lesions involved the upper tract and the terminal bronchioles, atria and alveoli. In the literature, the only similar conflagration injuries were reported from a German munition factory in 1917; this was associated with a flash fire with heavy smoke among women filling hand grenades, and the mortality was 50 per cent.

Lesions in the victims comprised minor visible burns, including the nares, and pseudomembrane formation in the larynx and upper trachea; there was less effect in the lower trachea but in some cases, necrosis of the bronchial walls and pseudomembrane formation was present. Lesions of the lung parenchyma were focal, but with hemorrhage and fibrin formation in most cases rather than purulent bronchopneumonia. The polymorphonuclear reaction was less than expected, as though negative chemotaxis was being exerted. Nonoccluding thrombi in veins were frequent. Occluding venous thrombi with infarcts were present in 3 cases. The victims who survived the first few days tended to show only slight lesions (injection and hemorrhage) of the upper tract; the lungs evidenced massive edema in some cases, but focal lesions of the terminal bronchioles and parenchyma were found in all dying within twelve days after the fire. The lungs in general were distended, atelectasis was not marked, the bronchi were dilated, air was trapped focally and there was less emphysema than expected.

Dr. Valy Menkin in discussing the paper stated that the findings were characteristic of the necrosin effect, with necrosis and fibrin thrombosis of veins. The liberation of euglobulin was, he thought, responsible for the bed fever. The absence of marked neutrophilic infiltration did not mean the absence of an acute inflammatory process but was a phenomenon of gradation. Possibly lactic acid formation prevented the emigration. Dr. Leary stated that, although the neutrophilic reaction was not the usual type of response, the lesion was nevertheless inflammatory in type. In response to a question by Dr. Reuben Z. Shultz concerning the type of injury seen in cases of immediate death, Dr. Leary said that death was due to carbon monoxide poisoning with injected overdistended lungs.

The last paper was by Dr. Alan Moritz and was entitled "An Experimental Study of Thermally Induced Injuries of the Lungs and Air Passages of Dogs." Dry and moist air at initial temperatures varying between 100 and 1000°C. was conducted to the larynx of anesthetized dogs through an insulated glass cannula. By means of an electrical heating unit, the inner wall of the cannula was maintained at a minimum temperature of between 100 and 125° C. to reduce heat loss between the external source of heat and the larynx. In some experiments the inhalation of hot air occurred incident to the normal respiratory activity of the animal, and in others hot air was forced into the lungs by a pump in such a way as to simulate the rate and amplitude of respiration. Thermocouples were placed in the larynx and at the bifurcation of the trachea to record the temperature of the inhaled air.

It was observed that moist air at 100°C. was more likely to produce pulmonary injury than dry air at 1000°C. Even with an initial external temperature of 1000°C., dry air was cooled to between 500 and 600° at the larynx and to between 60 and 80° by the time it reached the bifurcation of the trachea. The principal if not the only pulmonary changes produced by the inhalation of hot dry air were hyperemia and focal atelectasis due to the aspiration of detached masses of necrotic tracheal mucous membrane.

Superheated moist air (100 to 125°C.) produced direct pulmonary injury in the form of a necrotizing bronchitis with interstitial and intra-alveolar pneumonia of the central portions of all lobes, interstitial and intra-alveolar hemorrhage, and pulmonary edema.

In normal circumstances the inhalation of superheated air, dry or moist, would not be expected to produce significant pulmonary disturbance except in association with severe burns of the skin and of the mucous membranes of the nose or mouth and an obstructive edema of the larynx. Pulmonary injury not associated with burning of the skin of the face and of the mucosa of the nose and mouth, or with laryngeal edema, is not likely to be of thermal origin.

In response to a question concerning the length of exposure, Dr. Moritz said that with heated air, the exposures were up to 100 respiratory cycles over a period of four to seven minutes. With steam, the exposures were approximately forty seconds. In answer to another question, he stated that the effect of hot air was greatest in the upper portion of the trachea, where the heat was given up most rapidly. There was also considerable discussion about the location of the edema of the larynx. In animals, Dr. Moritz found the picture to be variable, depending on the amount of areolar tissue present in the different areas. This tissue is especially loose on the esophageal surface of the larynx. Dr. Leary stated that, in his experience, the most marked edema in man was on the aryepiglottic folds.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Life Is Too Short: An autobiography. By C. Kay-Scott (Frederick Creighton Wellman, M.D.). 8°, cloth, 348 pp. Philadelphia: J. B. Lippincott Company, 1943. $3.50.

This is an autobiography of a physician who went to Africa as a young doctor and remained there to study tropical diseases, compete with witch doctors, hunt big game, explore and survey where no white man had been before. From Africa, Dr. Wellman went to Europe and later to South America, finally returning to America.

A History of Tufts College Medical School. By Benjamin Spector, M.D., professor of anatomy and professor of the history of medicine, Tufts College Medical School. 8°, cloth, 414 pp., with 49 illustrations. Boston: Tufts College Medical School Alumni Association, 1943. $5.00.

This history is fully documented and is illustrated with a large number of appropriate pictures. An appendix contains photographs of the deans and the heads of the various departments of instruction, past and present, ninety-seven persons being included in this group.

1944 Daily Log for Physicians. Champaign, Illinois: Colwell Publishing Company, 1943. $6.00.

This standard account book for physicians has been issued in its usual format for the year 1944. Of particular interest is the comparative income schedule, considered a short cut to accurate figures for income-tax purposes. The 1944 edition also contains a new form for nonprofessional deductions—that is deductible expenses that are personal in origin and should not be included in professional expenses.

A Surgeon's World: An autobiography. By Max Thorek, M.D. 8°, cloth, 410 pp. Philadelphia: J. B. Lippincott Company, 1943. $3.75.

This is the autobiography of a successful surgeon who grew up in the Old World and made his mark in Chicago.

NOTICES

ASSOCIATION OF MILITARY SURGEONS

A meeting of the Association of Military Surgeons of the United States will be held at the Pennsylvania Hotel, New York City, November 2 to 4. In addition to addresses by the Surgeons General of the Army, Navy, and United States Public Health Service and by other distinguished guests, there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

(Continued on page xv)

NOTICES (*Continued from page 748*)

AMERICAN CONGRESS
OF PHYSICAL THERAPY

The twenty-third annual scientific and clinical session of the American Congress of Physical Therapy will be held September 6 to 9, at the Hotel Statler, Cleveland, Ohio. The annual instruction course will be held from 8:00 to 10:30 a.m., and from 1:00 to 2:00 p.m. during the days of September 6, 7 and 8. The scientific and clinical sessions will be given on the remaining portions of these days and evenings. All these sessions will be open to the members of the regular medical profession and their qualified aids.

For information concerning the instruction course and program of the convention proper, address the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago 2.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 22

SATURDAY, JUNE 24
*10:00-11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.
MONDAY, JUNE 26
*12:15-1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.
TUESDAY, JUNE 27
*12:15-1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
WEDNESDAY, JUNE 28
*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

JUNE 16. Boston Dispensary. Page xi, issue of June 8.
JUNE 21. New England Pediatric Society. Page xi, issue of June 8.
SEPTEMBER 6-9. American Congress of Physical Therapy. Notice elsewhere on this page.
SEPTEMBER 11-14. International Association of Industrial Accident Boards. Boston.
OCTOBER 3-5. American Public Health Association. Page ix, issue of March 30.
NOVEMBER 2-4. Association of Military Surgeons. Page 748.

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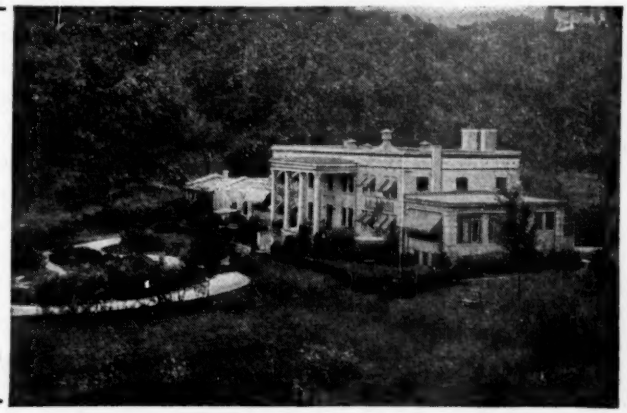

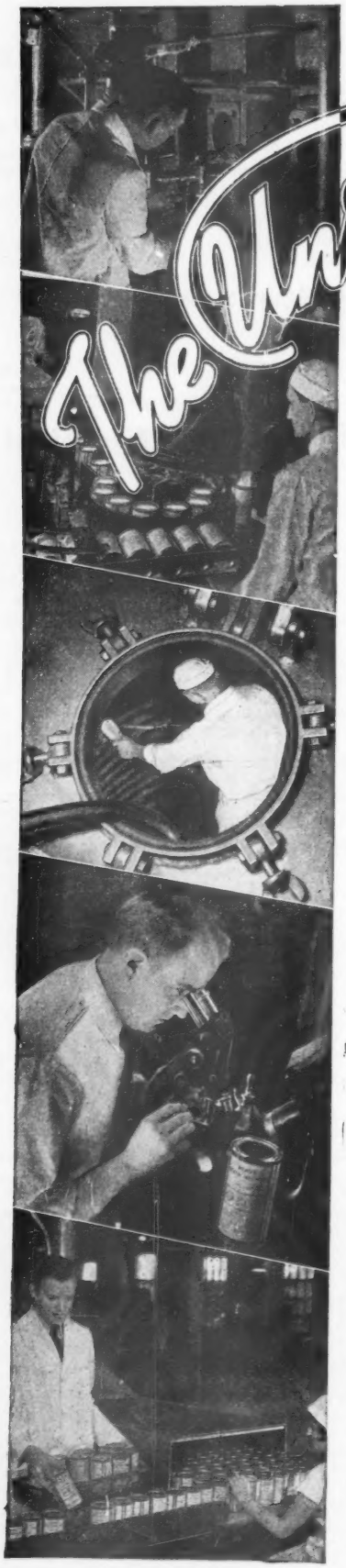

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